CLINICAL STUDY PROTOCOL

A PHASE 2, MULTICENTER, OPEN-LABEL STUDY OF DS-8201A IN SUBJECTS WITH HER2-EXPRESSING ADVANCED COLORECTAL CANCER [DESTINY-CRC01)

DS8201-A-J203

IND/EudraCT NUMBERS:136179/2017-003466-28

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VERSION 5.0, 03 JUL 2020

DAIICHI SANKYO

INVESTIGATOR AGREEMENT

A PHASE 2, MULTJCENTER, OPEN-LABEL STUDY OF DS-820IA IN SUBJECTS WITH HERZ-EXPRESSING ADVANCED COLORECTAL CANCER

[DESTINY-C'RCOI]

Spons()t Approval:

This clinical study protocol has been reviewed and approved by the Daiichi Sankyo repre.sentative lis1ed below.

PPD

Print Name | **Signature**

Clinical Study Lead

TItlr | **Datt (DD '-t\D[YYYY)**

Investigator's Signature:

I have fully discussed the objectives of this sn1dy and the contents of this protocol with the Sponsor's representative.

I tmderstand that i.nfomiation contained in or pertaining to this protocol is confidentila and should not be. disclosed, other tha n to those direc tly involved in the execution or the ethical review of the study, without written authorization from the Sponsor_ It is, however, pennissible to provide infomiatiou to a subject in order to obtain consent.

I agree to conduct this study according to this protocol amt to comply with its requirements, subject to ethical and safety considerations aud guidelines, and to conduct the study in accordance with the Declaration of Helsinki , International Council for Hannonization Guidelines on Good Clinical Practice (ICH E6), and applicable regional regulatory requirements.

1 agree to make available to Sponsor personnel. their representatives and relevant regulato1y authori ties , my subjects' sn1dyrecords in order to verify the data that I have entered into the case repo11 fom1.s I am aware of my responsibilities as a Principal h1vestigator as provided by the Sponsor.

1 understand that the Sponsor may decide to suspend or prematurely terminate the study at any time for whateve r reason; sucl1a decision will be communicated to me in writing. Conversely, should I decide to withdraw from execution of tl1e study, [will communicate my intention imm edia tely in w1iting to the Sponsor.

Pai nt l'i■mf | **Sigutun**

Tita. | **Date** (DD '.'.U1DlYYYY)

PROTOCOL SYNOPSIS

EudraCT:	2017 -003 466-28
IND Number:	136179
Protocol Number:	DS820l-A-J203
Investi gational Product	DS-820la
Active lngredients /JNN:	DS-820 la consists of au antibody component. tvLi\..A.L-900 I, c-0vale11tly conjugated via a maleimide tetrapeptide linker. to a drng component, 'MAAA-l18la.
Study Tit.le:	A Phase 2, multicenter, open-label study ofDS-820la in subjects with HER2-expressing advanced colorectal cancer[DESTINY-CRC0l]
Study Phase:	Phase 2
IndicationUnder hwestigation:	Human epidenua l growth factor receptor 2 (HER2)-expressing advanced co]orectal cancer
StudyObjective:	Ptimai:y Objectives: • To detenuine tl1e object ive response rate (ORR) of DS-820la in HER2-positiveadvanced metastatic colorectal cancer patients (Cohort A). Secondary Objectives: • To evaluate duration of response (DoR). disease control rate (DCR), progre·ssion-free survival (PFS), and overall survival (OS).. ORR assessed by the investigator is also eva l uated.. • To eval u ate ithe safety ofDS-8201a • To detennine the phannacokinetics (PK) of DS-820 la
Study Design:	This is a multic.enter, open-label, 3 cohorts, Phase 2 study to investigate the safety aud efficacy of DS-820la in BER2-expressing advanced colorect.al cancer subjects.. **Cohort A** Approximately 50 subjects with HER2-positive (immnolstochemistry[IHC] 3+ or IHC 2+/in situ hybrid ization [ISH] +) advanced colorectal cancer in single ann. Sponsor monitors the data after at least 20 subjects completed tu mor asses.sment at 12 weeks in Coh011 A. Cohorts B and C will be opened depending on the ass essm ent of benefit and risk obse1ved in the program.

	Cohorl B Approximately 20 subjects with HER2 IHC 2+/ISH - advanced colorectal ca, ncer **Co h o 1·tC** Approximately 20 subjects with HER2 JHC I+ advanced colorectal cancer
Study Duration:	Em·ollment is planned to occur over approximately 18 months, and treatment and follow-up is projected to be comp)·eted within approximately 6 mouths thereafter. Anticipated duration of the study is at least 24 months.
Shady Sites and Location:	Study sites in Japan, No1th America, and Europe.

Subje.ct Eligibility Crite1ia: Key Inclusion Cri teria:

1. Age 20 ye.ars old in Japan , 18 years old in other countries.
2. Pathologically documented unresectahle, recum nt,or metastatic colorect-al adenocarciuoma. Unti l spousor's notification to tl1e study sites, subject must be a RAS/v-raf muriue sarcoma viral oncogene homo)og Bl (BRAF) wild-type cancer.
3. ,Received a t least 2 prior regimens of standard treatm ent .
   - TI1e following therapies must be inc1uded in prior line5 of therapy;
     a. Fluoropyrimidine, irino tecan, and oxaliplatin
     b. hi subjects ⌞Ni tb R..i\S wild-type, anti-epidenu al growth factor receptor antibody.
4. Is wilting and able to provide an adequa te archival tumor sample available for tissue screening of HER2 status by Central Laboratory. If any anti-HER2 t11erapies (including pan-humanepidermaJ growth factor receptor agents and study dmgs) were received, tumor samples used should come from post anti-HER2 therapy.
5. Appropriate HER2 expression assessed by **Central** Laboratory per Cohort se tting

   Cohor t A: HER2 IHC 3+ or IHC 2+/ISH+.

   Cohort B: HER21HC 2+/ISH- .

   Coho1t C: HER2 IHC 1+.
6. Presence of at least one measurable lesion asse.ssed by the investiga tor per Res ponse Evaluation Criteria

in Solid Tumors (RECIST) version LL

7. Has eastern Cooperative Oncology Group performance status (ECOG PS) of O to 1.
8. Has left ventricular ejection fraction ::::50%
9. Has adequate organ function defined as:

Pnrnmrter	Laboratory value
Ade()Juat e bone marrow function	
Platelet count	I00.000/mm³ (Platelettransfusion is not allowed witJ1in 1 week ptior to screen.mg assessment)
Hemog]obin	:::9.0 gldL (Red blood cell transfusion is not allowed within 1 week prior to scree ning assessment)
Absolute neutrnphil count	?'.l 5 00 /mm ³ (granulocyte-colony stim ulating factor [G-CSF] administration is not allowed within 1 week prior to screening assessment)
Adequate renal function	
Creatm.ine	Creatinine clearance 30 mI.Jmin, as calculated using the Cockcroft-GaJut equation (Sectioo 17.I)
Ade(])uate hepatic fu nc tion	
Alanine aminotra nsfe rase (ALT), Aspartate amino transferase (AST)	**5** x upper Jim.it of nonnal (ULN)
Tota] bilimbin	**1.5 x** ULN if no liver metastases or < 3 x ULN in the presence of documented Gilbe1t's Syndrome (unconjugated hype rbilim binemia) or liv e r metastases at baseline
Adequate blood dotting function	

hnemational **normalized ratio/Prothro111bil1 time** and activatedpartial **tluomboplastintime**	1.5 x ULN

10. Male and female subjects of reproductive/cilildbearing potential must agre<: to folJow instmctions for method(s) of contraception.

Key Exclusion Criteria

1. Medical history of myocardial infarctjon witl1in 6 months before enrollment (study treatmen t), symptomatic congestive heru1 failure (New York Hea11Association Class II to IV, Section 17.4), troponiu levesl consistent with myocardial infarction as de fined according to the mauufactmer 28 days prior to enrollment (study treatment)
2. Has a coa-ected QT interval (QTcF) prolongation to >470 ms (females) or >450 ms (males) based on average of the screening triplicate 12-lead elect rocardiogram (ECG).
3. Has a history of (non-infectious) ILD/pneumonitis tbat required steroids, has cmrent ILD/pneumontiis. or whe re suspected ILD/pueumouitis cannot be mled out by itnaging at screening.
4. Has clinically significant comeal disease.
5. Has spinal cord compres5ion or e-linicaJly active central nervous system metasta,s-es defined as untreated and S}'mptomatic, or requiring therapy with corticosternids or anticonv ulsants to control associatedsymptoms. Subjects with clinically inactiv e brnin metastases may be included in the study.

Dosage Form, Dose and Route of Administratio n:	The DS-820la product is provided as a lyophilized powder containing 100 mg of DS-8201a in a glass vial (Lyo-DP). DS-820 la will be administered as an intravenous solution. Subjects will receive the 6.4 mg/kg of DS-820la on Day 1 of each cycle, once every 3 weeks.
Study Endpoims:	**P1·imary Endpoint:** • ORR assessed by the independent central imaging facility review b.tsed on RECIST version 1.1 in Cohort

A.

Secomlary Endpoints:

- Efficacy Endpoints (based on central revie\v unless otherwise stated):
  - ORR based on RECIST version 1.1 in Cohorts B andC'
  - DoR
  - OCR
  - ORR assessed by the investigator based on RECIST version 1.1
  - PFS
  - OS

Ex}loratory End}0 Lots:

- Time to response
- Best percent change in the sum of the longest diameters of measurable nuuors

Safety Endpoints:

- Seti ous adverse events
- Treatment-emergent adverse events (TEAEs)
- Physical examina t:i,on findings (:incl uding ECOG **PS)**
- Vital sign measurements
- Standard clinical la boratory parameters
- ECG parameters
- Echocardiogam/mul ti gated acquisitionacquisition findings
- Ophthalmologic findings
- Anti-dmg antibodies (ADA)

PK en<lpoints (DS-820la, total anti-HER2 antibody, and **MAAA-118** la):

- PK parameters: Cmax., Tmax. and AUClast. and other para meters will be calcu lated if appropriate.
- Senun couceutrations.

Biomal·ker endpoints

	• Se nuu extracellular domain of HER2 • Biomarker analysis using cell free deox)'Tibonucleic acid • Analysis of biopsies for mechanisms of resistance to DS-82 01a • Maikers of prior COVID-19 infection
Plami.ed Sample Size:	Tue total planned number of subjects is 90. Coho1t A: 50 Cohort B: 20: and Cohort C: 20
Statistical Analyses:	The primary analysis will bepe1foillled after <tll s ubjects have either discontinued the study or at least completed tumor assessment at 18 weeks in Cohort A. Effic.acy analyses: Perfo1rned for all subjects that who rec ei ved at least 1 dose of study dm g. TI1e primary efficacy endpoi11t is ORR assessed by independent radiologic facility review. TI1e point estimate of ORR and its 2-sided exact 95% confidence interval (CI) will be provided using Clopper-Pearsou method by cohort. TI1e sec o ndary efficac y endpoints are DoR, OCR, PFS (based on central assessments unless o therwise stated), and OS. ORR asses sed by the in vestigator and OCR will be analyzed in the same manner as theprimaryORR analysis. DoR, PFS, and OS will be summarized using Kaplan• Meier methodl by coho rt with median event times and tbeil'2-sided 95% Cls using Brookmeyerand Crowley method. Safety a11alvses: Safety analyses in general will be descriptive and wiU be presented in tabular format with the appropriate s1.uu m,uy statistics by cohott. PK anaJyses: Semm concentrntions for DS-8201a, total anti-HER2 an tibo dly and .MAAA-1181a will be listed, plotted, and summaized using desc lptive statistics by coho11 at each time point. PK parameters will be listed and summ arized using descriptive statistics by cohort. Populatfon PK and PK-PD modelit1g will be conducted and reported separately.

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LIST OF ABBREVIATIONS

ABBREVIATION	DEFL\"ITIO
AC	Adjudicalion Co11m1ittee
ADA	anri-drng antibodies
ADC	anribody-dn1g conjugate
[redacted]	
AE	adverse event
AES!	adverse eventsof special interest
ALT	alanine aminotransfease
AST	aspa rtate amino transfe rase (transaminase)
AUC	area under the plasma/sen m concenttatio-time curve
AUC0.21d	a-rea under the plasma/senun c once1m a rion-t ime cU1ve up to Day 21
AUCinf	area 1mder the plasma/s enun c oncem ration-time curve up to infinity
AUClasr	area 1mder the plasma/senun c oncenn-arion-t im e c\llve up to the last quantifiable time
BI	before tn fu.-,1011
BRAF	v-raf murine sarcoma viral oncogene homolog BI
BSEP	bile salt expon pump
dDNA	cell fl"ee deoxyribonucleic acid
CHO	Chinese hamster ovary
CI	confidence inte.rva)
CL	total body clea rance
Cmax	maximum plasma/semm concentratiou
COVID-19	coronavirus disease 2019
CR	completeresponse
CrCI	creatin ine clearance
CRF	as repo11 fonu
CRO	contract research organization
CT	computed tomog raphy
CTCAE	Common Terminology Critetfa for Adverse Events
CYP	cytochrome P450
DAR	drug-to-atibodyratio

ABBREVIATION	DEFI TI IO
DCR	disease conl:rol rate
DLT	dose limiting roxicity
DoR	duration of res pon se
DS 1	drug substance manufacntred using MA.AL-90O1 produced using the CH[redacted]
DS2	dmg s ubsta nce manufach1red using MAAL-900 I produced nsing the CH<[redacted]
EC	Ethics Conunittee
ECG	elecrrocardiogram
ECHO	echocardiogram
ECOGPS	Eastern Cooperative Onco logy Group perfonnance status
eCRF	electronic case report fonn
EOC	elecrronic data capmre
EGFR	epidennal growth factor receptor
Elli	ExpɔureIn Utero
EOI	end of infusion
EOT	end ofrrearment
EU	Eurnpean Union
FAS	full analysis set
F,U	follow-up
GCP	Good Clinical Practice
G-CSF	granu!ocyte-colonystimulating facror
HER2	human epidermal growtb factor receptor 2
HER2ECD	extracellular domain ofHER2
hERG	bwnan ether-a-go-go-related geue
HIV	human immunodeficiency virus
HRT	hormone replacem ent therapy
JB	Iuvestigator's Brochure
!CF	info1med consent fonn
ICH	International Council for Harmonisation
IHC	illllllllllObistochemistry
ILD	inler s tfrial lung disease
INN	i n temarioo.al non-proprietary name
INR/PT and aPTT	Intemational uonna.lized ratio/Prothrombin time and activated partial. thromboplastin time

ABBREVIATION	DEFI TI ION
1RB	institutional review board
!SH	in sin1 hybridizarion
IV	intr-avenous (ly)
IXRS	interaclive web response system
KRAS	human Kirsten rar sarcoma viral oncogenehomologue
LVEF	left veutti, ular ejection fraction
:tvlAAA-l l81a	the drug component of DS-82Ola - a derivat1ve of exatecan. a topoisomerase I inhibitor, fi'ee fonn
MAAL-9001	the antibody component of DS-820Ia - a humanized anti-HER2 immunoglobulin Gl monoclonal antibodyproduc d in-house with reference to the same amino acid sequence oftrasnizuw.ab
MATE	multidrug and toxin extmsion
mCRC	metastatic colorectal cane.er
MedDRA	Medical Dictioua1yfor Regulatory Activities
MRI	magnetic resonance imag:ing
mRNA	messeuger **RNA**
rvrro	maximum 101.erated dose
MUGA	muJtigated acquisition (scan)
NCI	NationalCancer Instimte
NE	not evaluable
NSAID	nonsteroidalanti-inflammatorydrug
OAT	organic anion transpo1ter
OATP	organic aniou transporting polypeptide
OCT	organic cation transporter
ORR	objective response rate
OS	**overall sm-viva1**
PD	prngre ss ive d isease progression-
PFS	free smvival
PK	pbannacokinetic(s)
pop-PK	populationphammcokiuetics
pop-PK/PD	populationpb.armacokine1ic s/phannacodynamics
PR	partial response
PT	Preien-ed Tenn
Q3W	once eve1y 3 weeks
QTc	corrected QT interval

ABBREVIATION	DEFI TIIO
QTcF	corrected QT interval by F1idericia's fom1ula
RA.S	rar sarcoma viral oncogenes homolog
RECIST	Response EvaluationCriteria rnSo lid Tumours
RP2D	recommended phase 2 dose
RT-PCR	real-lime polymerase chain reaction
SAE	serious adverse ewnt
SAP	statistical analysis plan
SARS-CoV -2	Severe Acute RespiratmySyndrome Coro navi ms 2
SA VER	Serious Adverse Event Repo11
SD	stable disease
SLD	**sum** of the longest diameters
SMQ	Standard MedDRA Query
SOC	system organ class
SOP	stan dard opera ting procedure
Sp0 2	peli phera l oxygen sattu·ation
SUSAR	Suspected Unexpected Serious Adverse Reaction
tu2	ten uinal elimination half-life
TBL	total bilirnbin
T-DM1	trastuzumab emtausine
TEAE	treatment emergent adverse event
Tmax	time to reach maximum plasma/serum conceutrntion
ULN	upper limit of uonnal
Vss	volume of distributionat thesteadystate

1. INTRODUCTION

1.1. Background

Colorectal cancer is the third most common cancer \.vorld \.vide theie were approximately 1.36 million new cases diagnosed and 690,000 deaths worldwide in 2012.[1] Several standard therapies for advanced or metastatic c-0lorecral cancer aJe listed in the guiddines [2,3] •1' , however. the treatment benefit of third line or subsequenttherapy is limited in patients who maintain their good perfom1ance status after receiving available treatments.

Because of djfferences in examination. methods and objective criteria, the reported frequency of Human epidermal growth factor receptor 2 (HER2) amplification and overexpression in colorectal cancer varies between studies.[5] In the HERACLES sn1dyto assess the antitumor activity of trastuzumab and lapatinib in patients \Vi th HER2-positive colorectal cancer, 5% had HER2-positive tumors in human Kirsten rat sarcoma vi.ral oncogene homo]ogue (KRAS) wi]d-type colorectal cancer[6]. hi the report from the analysis of 3256 patients enrolled in the QUSAR, FOCUS, and PICCOLO studies, it was repo11ed that HER2 overexpressiou iI1KR AS/v-raf mmi ne sarcoma viral oncogene homolog Bl (BRAF) mutated colorectal cancer tumor was l. 0%.[7] HER2 gene amplification is considered to be associated with resistance to anti-epidem1algrowth factor recept01(EGFR)-targeted tllerapy[8] and HER2 amplification is a predictive marker of shorter progression-free smvival (PFS) after anti-EGFR antibody cenndma.b treatment in patients with metastatic colorectaJ cancer (mCRC)harboring wild-type rat sarcoma viral oncogenes homolog (RAS) and BRAF.[9] Therefore, HER2 is considered to be an impo11ant target for mCRC, however no HER2-targeted therapies are approved for colorectal cancer.

DS-820la is au autibody-drng co1\jngate (ADC) targeting HER2. In the ongoing Phase l clinical study. DS8201-A-J10,1in subjects with advanced solid tumors, DS-820la was well tolerated at repeated doses ofup to 8.0 mg/kg intravenously (IV) once every 3 weeks **(Q3Vl}.**

1.2. Investigational Product

1.2.l. DescrlpOon

DS 820la consists of an antibody component. MAAL-900L covalen tly conjugated via a maleimide tetrapeptide linker. to adrug component, MAAA-l 81a. :MAAL-9001 is an in-house humanized immunoglobulin Gl monoclonal antibody with the same amino acid sequence as tra.stuzumab. MAAA-118 la , an exateea11 deriva tive , is a topoisomerase I inhibitor that is cell-membrane pe1meable, and more potent than SN-38 (active metabolite of irinotecan). This ADC achieves a high dmg to antibody ratio (DAR} (7 to 8) with homogeneous conjugation with MAAA- J 18la. DS-820la is cleaved by Jysosomal enzymes and releases lvL\.A.A118 lam the cytoplasm after it binds to the HER2 receptor; and gets intemaHzcd iu tumor cells.

Toe DS-820Ia Pltase l clinical study, DS820l-A-Jl01, was initiated with the antibod y component, MAAL-900 1 , produced using the Chinese hamster ovary (CHO- cell line (DS1). To suppor.t1203 study. as well as co1mnercial developmem.transitionha s been

made to MA L-900l production using a **cHc:aicel]** line (D 2). Analytic co_mparison of the two cell hne produc ts hos shown comparnbTrr"ry across a wide range of vanables. lvlinor differences have beeu observed in ıcal1 rofile char *e* variants siz.e variant s Fc2RIIIA binding. FcRn biuding, [redacted]
- Following single IV adm1mstrahon o • _ a to cynomo gus mo . eys. mean Cwax of DS-820la was similar, while AUClast was approximately 22% lower, for D52 as compared to OSI. However.in:\ xeuografl model. no dit'fereuce was seen rto to xicity benl\'een the two products. DS-820 la drug product manufactured from CH ceU line material will be supplied to this study.

1.2.2. Nonclinical Studies

1.2.2.1. Pharmacology

DS-820la inhibits tumor growth mainly by topoisom erase I inhibitiou-derived DNA damage, and induces apoptosis by die payload that is released from DS-.820la after internalization in cancer cells via HER2.

Tue results of in vitro cell growth inhibitionstudies conducted using several cancer cell lines have shown that OS-820la has more otent :owth inhibition at1Z.ainst HER2- ositive cells [redacted] Moreov,er no gem bttrnn was observed in HER2-negative cells, thus confirming the HER2 specificity of DS-8201.a.

S imilarly, when the in vivo anfitumor activity of DS-820la in a tumor-bearing mouse model of a HER2-posihve gastJic cancer cell line (NCI-N87) was studied, it was confirmed that DS-820la exhibited o tent. dose-de endent antitumor activi with tumor regression, [redacted]

ill addition.in vivo studies in tumor-bearing mouse models have confnmed that DS-820la has antitumor activity even against HER2 low-expressing colorectal cancer tumors regardless of KRAS status, that are insensitive to other anti-HER2 therapies. Moreover, DS-820la demonstrated potent effi cac y iu mice mocnJated witb a mixture of HER2-positive and negative cells while traszumab emtasine (f-DMl) did. not, due to more poten t bystander killing and higher cell memlmme penueability of the coujugitted toxin .[10] .[11] The effect therefore supports the etlicacy of DS-820 Ia against ttunors witb HER2 heter oge neity.

1.2.2.2. Safet)' Pha rm11cology

h:J. monk e ys treated with single intravenous doses of DS-820l a, no effects on the cardiovascular system. the respiratory system, or the centra l nervous system were observed at dose levels up to 78.8 llllt1kg. In addition, in btnn:ui ether a-go-go-relate d gene (hERG) studies of MAAA-118 la. MAAA-1181a did uot inlJibi l the hERG cbaunel cmTent at concen trations of up to IO Jtmol/L (approxi mately 5000 ng/mL).

1.2.2.3. Pharmacokinetics and Drug Metabolism

In cyuomolgus monkeys , the totaJ body clearance (CL) ofDS-820la wasmuch lower than the hepatic flow. and ii dec l eaed as tbe dose iucrease cl suggesting a non-linear process. The volumeof distribution at steady state (Vss) was dose to the plasma volume. Both DS-820 la and the tota l antibody. bound and unbound antibody combined. exhibited similar

phanuacokinetics (PK) profiles, indicating that the majority of the administered DS-8201a circulates in plasmaunchanged. The plasma concentrations of MAAA-1181a, the dmg that is relea se from DS-820l a, were quite. low. The Cmax of DS-8201a for DS2 \.\'as s ta tistically comparable to that for DS l, but the AUClast of DS-820la for DS2 was about 22% lower than that for DSL No anti-DS-8201a anti bodies were detectedin any animals.

The plasma protein binding ratios of f\1.AAA-118la (10 ng/m.L to 100 ng/mL) were 90.3% to 92.5% in mice, 94.2% to 96.7% in rnts. 86.5% to 89.1% in monkeys. and 96.8% to 98.0% in humans.

TI1e in vitro release rates of tv[AA.A-1181a from DS-820 Ia in mouse, rat, monkey, and human plasma for 3 weeks were 3.9% or less. Cytochrome P450 (CYP) 3A4. was the primary CYP enzyme involved in the metabolism of1-·IAAA-118 la. No human-specific metabolites were detected in vitro.

I\lAAA-1181a did not exhibit any potential to inhibit CYP1A2, CYP2B6, CYP2C8. CYP2C9, CYP2C19, CYP2D6, or CYP3A (50% inhibitory concentration [ICso] >5 0 µmol/L). Iv1AAA-1181a did not exhibit any potential to induce CYP 3A4, C'YP1A2, or CYP2B6 at concentrations ofup to 30 im10l/L. MAAA-118l a did not inhibit organic anion transporter (OAT) 3, organic cation transporter (OCT) 1, OCT2, organic anion transporting pol)l)eptide (OATP) IB3. multidmg and toxin extrusion (MATE) 1, 'MATE2-K. P-glycoprotein, breast cancer resistance protein, aud bile salt expo1t pump (BSEP) (1Cso>30 uuol!L). Ivlt\AA-l18la inhibited OATl and OATPlBl ·with the JC50 values of 12.7 and 14.4 unol/L respectively, al though the valnes were much higher than the Cmax of ,t\,1AAA-118la in lnm1ans (9.25 ng/mL [0.019 µmol/L] at 8.0 mg/kg of DS-820l a). bl addition, OATPs appeared to contribute to the human hepatic uptake of MA.AA.-1181a.

1.2.2.4. Toxicology

In a study of intermittent intntvenous dosing of DS-820la in rats (Q3W dosing for 6 weeks), no deaths or moribund animals were fotmd at dose levelsup to 197 mg/kg, the maximumdose. The major obs erved findings \\ereteslicular and intestinal toxicity at dose levels of 20 mg/kg and greater, and lyrnphatic/bematopoietic, skin, incisor tooth toxic,ity and renal toxicity at dose levels of 60 mg/kg and greater. Except for the testicularand incisor tooth changes, these changes ,vere all found to recover.

In an intenuittent intravenous dosing study ofDS-820la in cynomo]gus monkeys (Q3W. 6 weeks), one female was sacrificedrnoribund at 78.8 mg/kg, the highest dose level tested. The major toxicity findings in this moribund animal were obseJved in the intestine, hematopoiteic system, skin. and kidney. l11ecause of the moribundity appeared to be the deteiiorated conditi n of the animaL which resulted from decreased bod y weigbt and food consump tion. as well as bone man-ow toxicity and intestinal toxicity. The major findings of toxic.ity in the smviving animals1.vere o bse 1ved in the intestine at dose levels of 10 mg/kg and greater. and in the lung. testes,and skin at dose levels of 30 mg/kg and grea ter. In addition, hematopoieric system toxicity, renal toxicity. and electrncardiograrn (ECG) abnormalities(s hortenedPR interval and corrected QT interval [QTc] prolongation) ,vere found at 78.8 mg/kg. Except for the pulm onary and skin toxicity (pigmentatin), these findings tended to recover.

Thus, as described above, the severely toxic dose in]0% of the rulimals (STDIO) .in a rat intermittent intravenous dosing study of DS-820la was found to be greater than

197 mg/kg. In the monkey snidy, due to obse1ved moribundity at 78.8 mg/kg and evidence of critical puimona1y loxicity (eg, interstitial inflammation and/or alveolar edema) in the smviving animals, it was concluded that the highest non-severely toxic dose is 30 mg/kg.

In an intermittent intravenous dose toxicity study of MA.AA-I 181a (once weekly dosing for 4 weeks), findings in the Iympbatic/hematopoietic system, iutesti1lal tract and comea. of the eye were obsetved at 3 mg/kg and greater in rats but there was no deaths or moribundity up to 30 mg/kg. Findings similar to those in rats were observed in cynomolgus monkeys at dose levels of 1 mg/kg and greater. In addition, 1 female monkey died and l male monkey was sacrificed moti bund at 12 mg/kg. Although effocts on the heart (focal myocardial cell degeneration/necrosis) were found in the moribund male along with the above-mentionedtoxicities, there were no abnonnal heart findings in the female that died, even though both animals exhibited worsening clinical conditions associated witll sustained decreases in food consumptio,nbone man-ow toxicity, and intestinal toxicity. These changes were considered to be the cause of death and mmi bundity . The conuuon adverse fmclings in both DS-820la and MAAA-l 18l a studies were intestinal and Jympbati/chernatopoietic system toxicities. For DS-820Ia treatmeut, pulruona1y, testicular. skin. and renal loxicities were observed while heart, liver. and corneal toxicities were found only ·when MAA.A.-118 la was administered.

In a human cross-reactivity study of DS-820la with a panel of human tissues, DS-820l a-related cell membrane staining was found only in t11e placenta. In a cross-react.ivity study of DS-820 la with selected c,11onrnlgus monkey tissues (eg, brain, liver. kidney, lung, heart , in testiues, lymphoid organs, testes, and skin), neither membranous nor cytoplasmic staining was noted in any tissues.

In an in vitro 3T3 NRU phototoxicity sh1dy, tvlAAA-l 18la was fmmd to be phototoxic to Balb/c 3T3 mouse fibroblasts. Howeve,rin an in vivo singledose phototoxicity study of MA.AA-118 la in pigmented rats, no phototox.ic. reaction was noted at 3 mg/kg, the highest dose tested. For additional nonclinical data supporting DS-8201a use in nonclinicaJ sn1dies, please reter to the cun-ent hwestigatoh Brochure (IB).

1.2.3. Clinical Experience

DS8201-A-J101 is a Phase 1. 2-pait . multicente.r non-randomized, open-label, multiple do se, first in human study of DS-8201a. The Dose Escalation pa1t (Pait I) was conducted to idenitify the maximum tolerated dose (MTD) or tl1e recommended phase 2 dose (RP2D) of DS-820la. and the Dose Expansion part (Part 2) is being conducted to confinn the safety, tolerability, and efficacy of DS-820l a at the:MTD/RP2D. DS-820 l a is infi.tsed intravenously into each subject on Day I of each 21 day cycle. Su jects may continue to receive DS-8201a Q3W at the discretion of the hlvestigators. until unacceptable tox..icity, progressivedisease. or withdrawal of consent. 11:ris study is on-going.

Part 1 enrolled subjects with advanced breast cancer and gastii c or gastroesophageal junction adenocarcinoma. Upon completio n of Part I with dete.nn ination of MTD/RP2D, Part 2 was started. Part 2 consists of multiple coho1st : subjects with T-DM1-treated HER2 overexpressing breast cancer (Pai1 2a); trastuzumab-treated HER2 overexpressing gastric or gastroesophageal junction adenocarcinoma (Patt 2b); HER2 low-expre.ssing breast cancer (Prut 2c); HER2 expressing other solid malignant tumor (Part 2d); **and** HER2 expressingbreast cancer (Part 2e).

As of 8 Jrn1e 20 17 , a total of 148 subjects, 24 iu Patt I aud 124 in Pait 2. have received DS-820 Ja in thi s st udy. In Part L no dose limiting toxicities (DLTs) were reported and the MTD was not reached. Two doses were chosen for expansion in Part 2: 5.4 mg/kg and 6.4 mg/kg. Overall efficacy results from all dose cohorts in Part 1 demonstrate an objective response rate (ORR) of 34.8%(8 of23) anddiseasecontrol rale (DCR) of9l.3% (21 of23). Preliminary resu]t from Pa112 demonstrates an ORR of 48.8% (41 of 84) and a DCR of85.7% (72 of 84). Among 148 subjects who have l'eceived DS-8201a across all pans and cohorts iin the study, the adverse events (AEs) that occurred in more than 20% of subjects were nausea (65%), decreased appetite (53%), vomiting (34%), platelet cotmt decreased (31%), anemia (28%), alopecia (26%). dfa1Thea (24%,) const ipa tiou (24%), neutrophil count decreased (24%), white blood cell count decreased (24%), and malaise (22%). Tue maj o1ity of the AEs were of Grade I or 2 severity; *52* of 148 subjects (35.1%) experienced Grade 3 AEs and 10 subjects (6.8%) experienced Grade 4 AEs as the worst grade experienced. As of 10 Apti l, 2 out of *5* evaluable patients with coiore.ctal cancer achieved pa1tial responses (PRs) aud 3 patients were stable diseases (SDs).

Refer to the cmTent IB for a smmna1y of prel iminary clinical study dlat a.

1.2.4. Summary ,of Clinical Pharmacoklnetle..s.

Preliminary PK data are available from 24 subjects in DS8201-A-J101 study. Tl1e study is on-going.

PK parameters of DS-8201a, total antibody and !vLI\.AA-118l a at 5.4, 6.4, and 8.0 mg/kg are shown in Table L1, Table 1.2, and Table 1.3.

Systemic exposme (Cmax and AUClast) to DS-820l a over 3.2 mg/kg tended to increase greater than dose-propottional. Te11ni11al elimination half-life (T112) also increasedwith dose, and flattened out in the 6.4 and 8.0 mg/kg cohorts. Following a single intravenous administration of DS-8201a at 6.4 mg/kg. peak senun concentration (Cmax) of DS-820la was achieved \\rit.h a median Tmax of 2.16 hours and mean T 112. of7.33 days. The vo lume of <lis ttibutionat steady st.ate for DS-8201 a was approximately 45 mL/kg to 70 nl.Llk g (approx im atin g plasma /serum vo lum e), suggesti n g that DS-8201a is primarily limited to the vas cular compaitment.

l11e total antibody profile is similar to the PK profile for DS-820la, and the PK parameters of total antibody were comparable to thos.e of DS-820 la.

Senun MAAA-1181a concen tra tions gradually incre-ase d and reached peak concentrations , vith longer time to reach Truax (6 to 7 hours, median Tm.ax) co mpared to those for DS-820Ia. The systemic exposure (Cmax and AUC as repo[ted. in ng/mL and ng day/mL , respectively) to fvlAAA-J 181a was much lowerthan that ofDS-820la (as reported in tg/ml and •g day/mL, respectively), "'·here DS-820la exposure was >10,000-fold to that of l\1AAA-118 la. The elimination (T1 12) appeared to be similar to that of DS-8201a. l11is retl ects the intrinsic stability of the linker when DS-8201a is in circulation systemically.

Table 1.1: Mean (± Standa rd Deviation) Pharmacokinetic Parnmeters of SMum DS-8201a FoUowln g th e Fll'St Dose

Dose (mg/kg)	c ,na.x (Jtg/ mL)	Tmar (h)	AUCla s l (1ig·clay / mL)	AUCl11r (µg ·da y/ mL)	Trn (d.ay)	CL (mll day/kg)	Vss (mL/kg)
5.4 (N = 6)	127 **(17.2)**	1.92 (1 ,92 , **2.16)**	**544 (165)**	590 (186)	6.03 ,(0603)	I0.I (3.96)	**75.2 (24.2)**
6.4 (N=6)	181 (33.1)	2.16 (1.44, 4.08)	901 (15.5)	1030 (209)	7.33 (1.64)	6.41 (1.12)	**58.6** (11.0)
8.0 (N=3)	**216 (52.0)**	1.92 **(I.92. :?.16**)	**914 (23.5)**	1020 (279)	6.9 7 **(0.357)**	8.17 (1.93)	**69.7** (L3. 1)

AUClast = area under the plasma concentration-tune curve up to the last quant1fiable.llle. AUCinf = area under the plasma concentration-time curve up to infinity, CL: total body clearance, C'max = maximun1 plasma concemration. N = umnber. T tn = ten:u:inalelimination half-life.Tmax = time to reach maximum plasma concenuatioa Vss: volwne ofdistribution at steady state.
, f eau.(s tandard deviation)
Tm.ix reported as mt>-dian (:min, max).

Table 1.2: Mean (± Standa1·d Deviation) Pha1·macokinetic Pan mete1s of Ser u m T otal Antlbody FoUowlng the Fl.rst Dose

Dose (mg/kg)	Cinax (11g/ mL)	Tmn • (h)	AUC last (lpl lay /mL)	AUCiof (1tg·rui •/mL)	*Tv* (day)
5.4 (N =6)	116 (13 9)	1.92 {1. 92 . 6.96)	609(151)	682 (172)	6.78 (2. 39)
6.4 (N=6)	146 (18 9)	3.84 (2.16, 6.96)	878 (97.1)	1050 (149)	8.25 (2.16)
8.0 (N =3)	178 (18.:'i)	2.1 6 (1.92.6.72)	1090 (213)	1270 (296)	7.3j(0.417)

AUC las t = are.a under the plasma concentration-tune cui-ve up to the last quantifiable tune, AUCiuf = area. wider the plasma concentration-time curve up to infinity. Cm.ax = maximtwi plasma concentration. N = munber. T ,n: = tenninal elimination half-life, Tmax= time to reach maximum plasma. concenrration
Mean (standard deviation)
Tmax reported as median (.min. max).

Table 1.3: Mlea n (± Stand a d Deviatio n) Pharmacokinetic Pa1amete1·s of MAAi\.-1181a Following the First Dose

Dose (mg/kg)	C:1n.·1.x (ug/mL)	Tma.x• (h)	AtiClast (ng·day/mL)	AlJCi.1.f (og·cla y/ mL)	Tl.l! (<lny)
5.4 (N =6)	10.8 (7.56)	5.28 (3.84, *23.i 6)*	40.6 (I 9.8)	43.6{21.2)	6.ll {0.811)
6.4 (N=6)	6.80(E.72)	6.72 (4.08. 7.20)	31.0 (5.11)	34.2{5.63)	6.28 (1.17)
S.0(N = 3)	9.25 (3.18)	6.72 (6.72, *6.96)*	39.4 (6.43)	43.4 (9.16)	*6.36* (1.53)

AUCla5t = area under the pla sma concentrauoo-tune curve up to the last quantifiable tune, AUCiuf = area under the pla5ma c.oncentration-time curve up to in:finity, Cm.ax= maximum plasma concentration. N = munber. T1n. = tenninal elimination half-life, Tmax =time to reach maximum plasma concentration.
Mean (standard deviation). Tmax repo1ddar; median (min. max).

1.3. Study Rationale

HER2 is a member of the human epidennal fac1or receptor superfamity that initiates sigual transduction via the PDK/AKT and RAS/!vL.\PK path ways.[12. 13] In human advanced solid tumors expression of HER2 protein has been reported in various tumor tissues and in a variety of cultured tumor cell lines including breast cancer.[14] gastric canc,er [1 5 16] **pancreatic** can cer .[17] luug cancer,[18] colorectal cancer,[19] and ova1ian cancer .[0]

HER2 amplification is an established target of treatments for patients with breast or gastric cancer. however no .anti-HER2 treatment is approved for colorectal cancer. Iu a HERACLES study to assess tile antitumor activity of trnst1.1Z1.m1ab and lapatinib in patients with HER2-positive co]orectal cancer refractory to chemotherapy and anti-EGFR antibodies, ORR was 30% (95% confidence intc1wl [CI], 14 to 50). DCR was 59% (95% C l, 39 to 78), and median PFS was 21 weeks (95% Cl. 16 to 32).[6] The systemic treatment for mC'RC. targeted treatments (anti-VEGf and if-RAS wild-type, anti-EGFR) are recommended during the cow"Se of their treatment especially for their first-line or second-line2.-,3 [4] HER2 amplification is predictive of shorter PFS afte1·cehiximab ti.·ealment in patients with mCRC ha1boringwild-type RAS and BRAF.[9] In the 3rd line or s ubseq uent thetap y, o ther the rapie,s indncling regorafenib, and TAS-102 are lisred in the gnidehne.2-[3 4] ORR ofTAS-102 and regorafenib are Oto 1.6%, and their PFS are 1.9 to 2.0 months [21. 22] Targeted agents such as reg.orafen ib, bave different toxicity profile and may fonif the usage of the agents based on pre-existing conditions. Therefore, both efficacy and safety advances are needed in the treatment approaches for patients with advanced colorectal cancer. and HER2 will *be* target for colorectal cancer patients.

DS-820la is a HER2-targeting ADC with a high DAR (7 to 8), and a novel topoisomerase I inhibitor. DS-820la is ex ected to inhibit tumor owth on the basis of the followin g reasons: [redacted] the MAAA-1181a that is released from DS-820 la after the internalization induces apoptosis by inhibiting topoisomerase I. Nonclinical evideuce demonstrates that the HER2 targeting of DS-8201a is ltighly specific. In a st udy conducted in tumor-bearing mouse models., DS-820 la has antitumor activity against HER2 expressing colorectal cancer palicul-de1ived xeuograft models regardless of e·ither HER2 level or KR..t\S stah ts. Thi s result suppo1ts to examine the efficacy with HER2 low expressi.ug s ubjects explora tor y.

In the Phase·! study, DS8201-A-J10l, the preliminary results as of 8 June 201, 7 indicates that DS-8201a has acceptable safety and PK profiles, and antitumor activity. There have been no reported DLTs. and MTD was not reached in the 0.8 mg/kg: to 8.0 mg/kg Q3W. and 5.4 m,g,'kg or 6 .4 mg/kg are considered to be a recommended phase 2 dose. In Part 1 of the Phase 1 study, several doses of DS-820la were administered for total 24 subjects and the ORR was 34.8% and the DCR was 91.3%. As of 10 Apri l, 2 out of *5* eva lua ble patients w ith colorectal cancer achieved. PRs. and 3 acb.ieved SDs.

Based on the non-clinic.al and the clitrical observations in the Phase 1 study (DS8201-A-Jl 01), DS-820la was well tolerated and effective in HER2-expressing colorectal cancer subjects. TI1erefore a Phase 2, multiceuter , open- la be l s tud y will be conducted to detennine the efficacy and safety profile of DS-8201a for HER2-expressing colorectai cancer. The study is illi1iated for subjects wi1hHER2 over-expressing subjects, aud the

explorntory cohmt for HER2 low expressed subjects will be opened after monitor the data of the 20 subjecst with HER2-overexpressing colorectal cancer.

1.4. Risks and Benefits for Study Subjects

Preliminary data suggests that DS-820 la demonstrated anti-nuuor activity with a small number of HER2-overexpre ssing colorectal cancer subjects (see Section 1.2.3).

Overall the reponed AEs in the DS820l-A-Jl 01 clinical smdy (see Section l.2.3) a1·e consis te n t with the safety profile of DS-820la. expec ted based on data available from nonclinical toxicology studies as well as drugs of similar class. Considering the frequency and biological plausibi lity of the AEs repo1ted, the following A.Es have been identified as adverse dmg reactions associated with the use ofDS-820la: nausea, decreased appe tite, vomi ting , platelet count decreased, anaemia, alopecia, dianhoea, neutrophil count decreased, white blood cell count decreased. Tbe majority of the treatment emergent adverse events (TEAEs) were of Grade 1 and Grade 2 severity. Bas ed on clinical data and safety infonuation available from other sources as of 13 Dec 2017 and tbe 2 fata l c.ases coufinned by the ILD AC as ILD and caused by DS-820la, ILD and pneurnoniti.s are added as adverse dmg reactions associated with the use of DS-8201a. Subjects receiving DS-8201a should be monitore d for signs and sym ptoms of any of the toxicities observed in nonclinical studies and to other products of the same cla<ss, which are discussed below.

In nonclinical toxicology studies. the intestinal toxicity, hematopoietic system toxicity, pulrnouaiy toxicity, testicular toxicity, skin toxicity. and renal toxicity were found in association with the administration of DS-820la. In add ition to these toxicities, similar to other products of the same class, the possibility of ca1diotoxicity, hepatotoxicity, embryo-fetal toxicity, or corneal toxicity occurring in subjects receiving DS-820 la cannot be excluded. Opbtbalmologic safe ty monito1ing, whicb includes visu al acuity. slit lamp ex.am, and fundoscopy will also be pa1t of the overa ll eval ua tion. These assessment ·will be pe1fo rmed at baseline and at specific inteivals described in the protocol and at the end of treatme,nt when an additional exam wil1 also be perfonned Moreover, at the discre tion of the investigator. opbtbahl1ologic testing can be peiformedat any time during the study.

For the DS-820la clinical program, based on the available pre-clinical data, review of the cunndative literntl.u-e, repo11ed toxicitie s for the sa me cl ass of agents and biological plausibi lity, the following events are cons idered to be ad ·ve rse events of special interest (AESI): Inters titial lung disease (ILD)/pneumonitsi, Cardiotoxicity (cardiac-related events including QT Prolongation and Left ventricular ejec ti on fraction (LVEF) Decrease). and I11fusiou re lated reactions.

ILD/ pneumouitis should be nded out ff a subject develops an acute onset of new or worsening pulmonary or other related signs/symptoms suchas dyspne,acougb or fever. ff the AE is suspected to be ILD/pneumonitis, study d:mg sho uld be inten1 1pted pending diagnostic evaluation, which should includ e bigh reso lu tion CT and pulmonologist c-0usultation, As soon as ILD/pueumonitisis suspected. corticosteroid u·eaunent sho uld be start ed promptly as per clinical treatment guidelines.

If the AE is confnmed to be ILD/pueumonitis, follow the managemen t guidance as described in Section 5.4. An ILD Adjudication Comm ittee (AC) is being established for the program and ,i ill review all cases of potentialILD/pneumonitis on an ongoing basis.

LVEF will be measured by either echocardiogram (ECHO) or muJtigated acquisition QvfUGA) scan. All ECHOslMUGAs will be evaluated by the Jnve.stigator or delegated ph ysician for monitoring cardiac function. Troponi:n will be me.as ured at screening and after each infusion and as needed based on subject reported cardiac symptoms. Triplicate ECGs will be petformed and standard ECG parameters will be measured, including RR, PR, QT inte1val,sand QRS duration.

As \Vitb any therapeutic antibodies, there is a possibility of infosion-related reactions. and immune responses causing allergic or anapbylactic reactions with administration of **DS-**820 Ia. Immune response causing allergic or anaphylactic reactions is considered to be an event of specia1 interest for DS-820lai clinical program. Subjects receiving DS-820la should be monitored vital signs. physical examination, monitor signs and symptoms of infusion related reaction: chills, fev,er hypotension, skin rash, etc.

Additional safety assessments should be conducted as needed, at the investigator• discretion. Hepatotoxicity. embryo-fetal toxicity, visua] disturbauces/comealtoxicity. or pbototoxicity occurring in subjects receiving DS-820la also cannot be excluded.

Based on the effic<1cy and s<1fety data observed in the nonclinical sh1dies, the clm ent cl i nical experience of the Phase I stuciiy and the information from other products of the same class, the benefit-risk balancesupports furtl1er clinical development of DS-820l a in this patient population. For up to date assessments of1isks and benefits to subjects, please refer to the current ill for DS-820la.

2. STUDY OBJECTIVES AND HYPOTHESIS

2.1. Study Objectives

2.1.1. P1·tmary O b jecti ves

- To deteunine the ORR of DS-820 1a in HER2-positive advanced metastatic colorectal cancer patients (Cohort A).

2.1.2. Secon cl.ar y Objectives

- To evaluate duration of response (DoR). DCR, PFS. and overal1 smvival (OS). ORR a%ess:ed by the in vestigator is also evaluated.
- To eva luate the safety of DS-820la
- To detennine the PK aud anti-drug antibodies (ADA) ofDS-820la

2.1.3. Explorato1·y Objectives

- To evaluate time to response
- To detenniue biomarker
- To eval uate ex posure-res ponse re lat ions hips for efficacy and safety endpoints

2.2. Study Hypotheses

DS-820la confers an ORR benefit in HER2-expressing advanced colorectal cancer patients

2.3. Study Endpoints

2.3.1. Prima1·y End1)ol.ot

ORR assessed by tbe independent radiologic facility review based on ResponseEvaluatio C1i te1ia in Solid Tumors (RECIST) version 1.1 lll Cohmt A.

2.3.2. Seconchu-y Endpoints

- Efficacy Endp oints(based on central1:eview unless otherwise stated):
  - ORR based on RECIST version L1 in Cohorts B and C
  - DoR
  - DCR
  - ORR assessed by the iuvestigator based on RECIST version 1.1.
  - PFS
  - OS
- Safety Endpoints will include:

- Serious adverse events (SAEs)
- TEAEs
- Physical examination findings (including Eastern Cooperative Oncology Group perfonnance status [ECOG PS])
- Vital sign measurements
- Standard clinical laboratory parameters
- ECG parameters
- ECHO/MUGA findings
- Ophthalmologic findings
- ADA

- PK Endpoints (DS-8201a, total anti-HER2 antibody and MAAA-1181a):
  - PK parameters: Cmax, Tmax, AUClast and AUC0-21d
  - Serum concentrations.

2.3.3. Exploratory Endpoints

- Exploratory efficacy endpoints:
  - Time to response
  - Best percent change in the sum of the longest diameters (SLD) of measurable tumors
- Semm extracellular domain of HER2 {HER2ECD)
- Biomarker analysis using cell free deoxyribonucleic acid (cfDNA)
- Analysis of biopsies for mechanisms of resistance to DS-8201a
- Markers of prior COVID-19 infe-ction

3. STUDY DESIGN

3.1. Overall Design

3.1.1. Overview

This is a multicenter, open-label, 3-cohort, Phase 2 study to investigate the safety and efficacy ofDS-820la in HER2-expressing advanced colorectal cancer subjects.

Cohort A is a single arm study and will enroll approximately 50 subjects with HER2-positive(immnohistochemistry [IHC] 3+ or IHC 2+/in situ hyb1idization [ISH] +), advanced colorectal cancer. Sponsor monitors the data after at least 20 subjects completed tmnor assessment at 12 weeks in Cohort A. Cohorts B and C will be opened depending on the assessment of benefit and 1isk observed in the program. and Sponsor will infonn to the study sites when Coho11s B and Care opened.

Cohort B will ew·oH ap proxim atel y 20 subje.cts witli HER2 Il-IC 2+/ISH - advanced colorectal cancer.

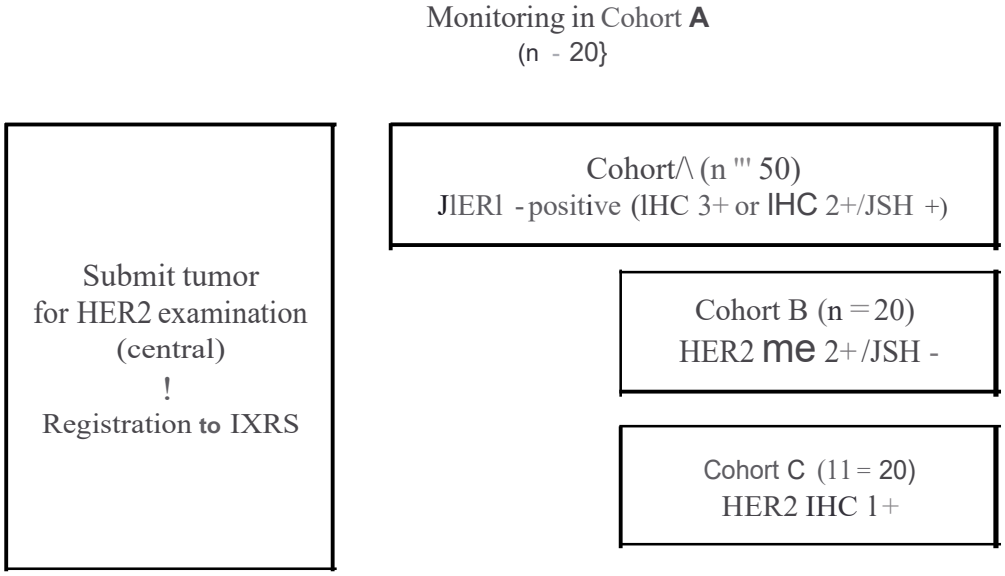
Cohort C ·will enroll approximately 20 subjects with HER2 IHC 1+ advanced colorectal cru1cer.

D S-820 1a will be administered as a sterile TV so lution at a dose of the 6.4 mg/kg every 3 weeks.

After obtaininga signed infonned consent fonn{ICF) for tissue screening from a subject, the tumor samples will be submitted to central laboratory to examine HER2 status for screening. TI1e subjec 1t whose ICF for study entry will be registered to interactive web response system (IXRS).

The study treatment will be continued according to the dosing cri.te1ia to derive clinical benefit in the absence of withdrawal of subject consent, progressive disease (PD), or unacceptable toxicity. If the study tre.atment is delayed more than 4 weeks from tbe planned date of administration, the subject will be \.Vithdra\.\'Il from the study (see Section 5.4).

Figure 3.1: Stucly Design Schema ofDS8201-A-J203



Coh011 Band Care opened after Sponsor's notification to the study sites.

HER2 = human 1:Pid 1111 .!ZIOWth factor receptor 2. IlfC = i.tmmmohis tochemistI)'. ISH = in sih1 hybrid ization. IXRS = interncth,-e web /voice response system

3.1.2. Domtlon of the Study

Enrollment is planned to occur over approximately 18 months, and treatment and follow-up (F/U) is projected to be completed approximately 6 months thereafter. Thus. the-anticipated duration of the study is at kast 24months.

Sponsor may terminate the study at any time and study tennination may also be requested by (a) competent authority(ies).

3.1.3. Duration of Subject Participation

Each cycle of treatment o f DS-8 2-0 1a will be 21 days. The number of rreatmeut cycles in this study is not fL'{OO. Upon commencing study treatment, subjects may continue receiving the study drug until the occnn ence of any of the events defined in Section 5.7. After discontinuation from study treatment, all subject s, regardless of whether they discontinued prior to or subsequent to disease progressio,nmay be contac.ted every 3 months llllltil death or until F,U data collection is no longer needed (at the sponsm's discretion), to obtain infonnatiou abo1llt subsequent treatment(s) and survival status.

3.2. Discussion of Study Design

It is estimated that approximately 90 subjects will be enrolled in the st11dy in No1h America, Japau, and European Union (EU).

3.3. Selection of Dose and Usage

Toe dose selection was based on the preliminary clinical data from Snidy DS8201-A-Jl01. DS-820la was administered at 0.8 mg/kg to 8.0 mg/kg Q3W in the Phase 1 st11dy and the MTD was not reached up to 8.0 mg/kg. In the 8.0 mg/kg coho11, 2 of 3 subjec ts

discontinued due to adverse events. ln the Pai1 2d. I1 colorectal cancer subjects received 6.4 mg/kg ofDS-8201a and 2 of them bad PR. On the basis of theefficacy, tolerability and PK profile es tablished in the Phase 1 study and non-clinical studies, the doseof 6.4 mg/kg Q3W wiU be used in this study.

4. STUDY POPULATION

Subjects must sign and date the infonued consent form provided by the study site before anystudy-specific. qualification procedures are conducted.

4.1. Inclusion Criteria

Subjects must satisfy **all** of the fo1lowi11g criteria to be included in the study:

1. Age 20 years old in Japan, 18 years old in other countries.
2. Pathologically docmnented unresectable, recun ent, or metastatic colorectal adenocarcinoma. Until sponsor's notificatim1 to the srudy sites, subjectmust be a RASJBRAF wild-type cancer.
3. Receive<1at least 2 p1or regimens of standard treaunent
   - 111e following therapies must be included in prior lines of therapy;
     a. Fluoropy lmidine, iri notecan, and oxaliplatin
     b. hi subjects ,..,ith RAS wild-type,anti-EGFR autibody.
4. Is willing and able to provide an adequate arcbival nuuor sample available for tissue screening to confirm HER2 stan1s hy Central Laboratory. If any anti-H ER2 therapies (including pan-human epidenna1 growth factor receptor agents and study dmgs) were received, tumor samples used should come from post anti-HER2 therapy.
5. App ropriate. HER2 expression assess.ed **by Central Laboratory** per Cohott setting

   Cohort A: HER2 IHC 3+ or IHC 2+/ISH+.

   Cohort B: HER2 IHC 2+/ISH-.

   Cohort C: HER2 IHC 1+.
6. Presence of at lea st **1** measurable lesion assessed by the investigator based on RECIST version 1.1.
7. Has ECOG PS ofO to I.
8. Has LVEF 250% within 28 days before emollment (study drug treatment).
9. Has adequate organ function within **14** days before emollment (study drng treatment), defined as:

Parnmete1·	**Laboratory value**
Adequate bone **marrowrnnc tlon**	
Platelet cotmt	?!1OO,OOO/mm^3 (Platelet transfusiou is not allowed within I week prior to scTee ning assessment)
Hemoglobin	'.2:9.0 gtdL (Red1>lood c.ell transfusion is nor. allo\ved wi thin I week prior to screening assessment)

Pam meter	Laborato11' valu e
Absolme lllc'uu·opltil count	**1500/uun^3** (G-CSF administration is oot allowed witui.u 1 week prio r to screening assessment)
Adrqnat renal function	
Creatinine	Creatiniueclearance ?'.:30 mL!min as calculated using the Cockcrft-Gault equation (Seciou 17.1)
Adequate ht patlc function	
Alanine aminoU<lllSferase (ALT). Asprutate a.minotransferase (AS1)	**:::5** x upper **limit ofnonnal (ill..N)**
Total bilir'ubin	**1.5** x **ULN ifno** livermetastases or < 3 x ULN **in the presence of docmnented Gilbei-t's Syndrome (unconjugated hyperbilirnbinemia)** or **liver metastases at baseline**
Adequate bloodd otting rnuction	
International nonualized ratio/Protluumlbin timeand activated partial thromboplastin time	**1.5** x **ULN**

10. Has adequate treatment washout period before em ollment (study treatment), defined as:

T1·e atmenf	Washout Period
Major surgery	4 weeks
Radiation therapy	;::4 weeks (if palliative stereomctic radiation theral}y withoutabdomina.J. 2:2 weeks)
Chemo therapy (incl uding antibody dt1ig. therapy, retinoid therapy)	;;:3 weeks (2:.2 weeks or 5 half-lives before smdy drug trearmeur, whichever is longer. for s111all-111o lecnletargetedagents sucb as 5-fluoromacilb-ased agents, folinate agents, weekly paclitaxel: :::4 weeks: Abs (eg. bevacizumab. cetuximab and pauinumnuab. ram uci mruab): 6 weeks for llitrostm as or m.itomycin C
Immunotherapy	2:4 weeks
Cytocfaome P450 (CYP) 3A4 sn·oog inhibitor. OATP inhibitor	:::3 elimination half-livesof the inhibitor

11. Male and fen.tale subjects ofr eproductiveichildbearingpotential must agree to use a highly effective fo1m of contrace ption or avoid intercourse during and upon completion of the study and for at Jeast 7 m onths fo r females and 4 months for

males after the last dose of study drng. Methods considered as highly effective methods of contraception include:

- Combined (estrogen and progestogen containing) hormonal coutraception associated with inhibitionof ovulation:
  - Oral
  - Int:ravaginal
  - Transdennal
- Progestogen-only ho1monal contraception associated with inhibition of ovulation:
  - Oral
  - Injectable
  - Implantable
- Intrauterine device
- Intrauterine honnoue-releasing system
- Bilateral tubal occlusion
- Vasectomized pa1tner
- Complete and trne sexualabstinence defined as abstinence when it is iu line with the prefened and usual lifestyle of the subject. Subjects in this study should refrain from heterosexual intercom:se during and upon completion of the sn1dy and for at least 7 months for females and 4 months for males after the last dose of study dmg. Periodic abstinence(e.g.. calendar, ovulation. symptothennal, post-ovulat ion methods), declaration of abstinence for the duration of exposure to study drng, and withdrawal are. not acceptable methods of contraceptio.n

Non-chlid-bearing potential defined as pre-menopausal females with a documented tubal ligation or hysterectomy; or postmenopausal defined as 12 months of spontaneous amenorrhea (in questionable cases, a blood sample,;i,rith simultaneous foJlicle-stimulatiug honnone >40 m.IU/mL and estradiol <40 pg/mL [<147pmol/L] is confinnatory). Femal.eso n honnone replacement therapy (HRT) and whose menopa usal status is in doubt will be1equired to useone of the contraception methods outlined for \.Vomen of child-bearing potential if they wish to continue their HRT during ,the study. Otl1erwise, they must discontinue HR.I to allow confinnation of post-menopausal st atus prior Ito s tudy emollment. For most fonns of HRT, at least 2 to 4 weeks wiU elapse behveeu the cessation of therapy and the blood draw: this interval depends on the type and dosageofHRT. Follo\.ving c.oruitmation of their post-menopausal status, they can resume use ofHRT during the study without use of a contraceptive method.

12. Male subjects must not freeze or donate spenn start ing at Screening and throughout the study period, and at least 4 months after the final study drug

administration. Prese1vation of spenn should be considered prior to enrolment in this study.

13. Female subjects must not donate, or retrieve for their own use. ova from the time of Screening and throughout tfu.e s tudy treatment period, and for at least 7 months after the final study dmg admi11istration.
14. Must have provided informed consent for sh1dy participation (see Section 15.3) before pe1fonnance of auy study-specific procedures or tests.
15. Subjects shouldbe able and willing to comply with protocol visits and procedures.

4.2. Exclusion Critet"ia

Subjects who meet any of the following criteria ·will be disqualified from entering th.e study:

1. Medical histo1yof myocardial infarction within 6 months before enrol.lment (s mdy treatment}, symptomatic congestive hea1t failure (New York He.art Association Class II to lV, Section 17.4), troponin levels cons istent with myocardial infarction as defined according to the. manufacturer 28 days p1ior to em·ollment (study treatment).
2. Has a corrected QT interval (QTcF) prolongation to >470 ms (females) or >450 ms (males) based on average of rbe screening triplicate 12-lead ECG. The QT intervals will be coriected for]1eart rate by F1idericia's formula (QTcF = QT/[RR]).
3. Has a history of (non-infectious)ILD/pneumouitisthat required steroids. has cun eut ILD/puemno n.itis, or where suspected IL1)/pueumouits cannot be nded out by imaging at screening.
4. Has c.linica ll y significant comeal disease in the opinion of the investigator.
5. Has spinal cord compression or clinically active centraJ nervous system metastases, defined as untreated and symptomatic, or requiring therapy with co11icoesrtoids or anticonvulsauts to control associated symptoms. Subjects wi.th clinically inactive brain metastases may be included in the study. Subjects with treated brain metastases tbat are no longer symptomatic and who require no treatment wid1 co1ticosteroids or anticonvulsants may be included in thestudy if they have recoveied from the acute toxic effect of radiotherapy. A minimum of2 weeks must have elapsed between the end of whole bra.in radiotherapy and study enrollme.ut.
6. Has multiple p1imary maligua11cies within 3 years, except adequately resected non-melanoma skin cancer, curatively treated in-situ disease, otl1er solid tumors curatively tre.a.te d.
7. Has history of severe hypersensitivity reactions to either the dmg substances or inactive ingredients in the dmg product.
8. Has an uncontrolld infection requiting IV injection of antibiotics, antivirals. or antifungals.
9. H:as s ubstance abuse or any other medical conditions that would incre.ase the safety risk to the subject or interfere witJ1 partic ipatio n of the subject or evaluation of the e-1111.ical study in the opinion of" the hwestigator.

10. Has known human immunodeficiency virus (HIV) infection, or active hepatitis B or C infection. Subjectsshould be tested for HIV prior to em·ollment (study trea tme nt) if requir ed by lo cal reg ulations or ins titu tion al revi ew board (IRB)/ethics committee (EC).
11. Has unreso lved toxicities from previous anticance r therapy, defined as toxicities (other than alopecia) not yet resolved to Grade 1 or baseline. Subjects with chronic Grade 2 toxicitiesmay be eligible per thediscretion of the Investigator after consultation with the Spo nsor Medical Monitor or designee (eg, Grade 2 chemoth erapy- induced neurop athy).
12. Is pregnan t or breastfeeding, or planning to become pregnant.
13. Prior tJ:eatment with an ADC which consists of an exatecan dle l ivative that is a topoisomeraseI inhibitor.
14. Social. familial. or geographical factors that would interfere with study pa1ti cipation or F/U
15. Has a concomitant medical condition that would increase the risk of toxicity, in the opinion of the investigator.

5. STUDY TREATrvIENTS

5.1. Assignin g Subj ects to Tr eatm ents and Blindin g

5.1.1. TreatmentGroups/Sequences

There will be subjects allocated to 3 different cohorts according to the HER2 status. Cohort A ·will be opened from the beginning and Cohmts B and C will be opened after the decision of the sponsor dlu-ing the sn1dy. All subjects will receive DS-820la treatment of the 6.4 mg/kg Q3W.

5.1.2. Method of Treatment Allocation

Subjects are registered! in IXRS and they are allocated to e:ach cohor1 according to the centrally continued HER2 status.

Cohort A

HER2-overexpressing(IllC 3+ or IHC 2+/ISH+)

Cohort B

HER2 rnc 2+/ISH -

Cohort C

HER2lHC 1+

5.1.3. Blinding

TI1is sh1dy is an open-label sn1dy and no blinding will be perfonned.

5.1.4. Emergency Uoblioding Procedun.

Not applicable.

5.2. Study Drug

5.2.1. Description

111e DS-820 Ia dmg product containing I00 mg of DS-820la is provided as a lyoph.il ized powder containing 100 mg of DS-820l a in a glass vial. Each glass vial should be reconstituted to a concentration of 20 mg/mL. Each vial is designed for single use only and is not to be used to treat more than 1 subject.

5.2.2. Labeling and Pac k aging

DS-8201a will be supplied by the sponsor. This will be clinicaJ labeled in compliance with the regulatory requirements aud packaged. U1e labeling or the packaging will clearJy display the name of the invest ig ational pro d uct, the investigational product manufacturing code, storage conditions and other re.quired information in accordance with local regulations.

5.2.3. P1·epa ration

Toe drug for IV infusionis preparedby dilution of tl1e required volwne of the dmg product calculated based on the subject's body weight. Prepared medicinal solutions should be used immediately. The prep aration will be conducted in accordance with **the** pharmacy instrnctions provided by the sponsor. Procedures for proper handling and disposal of anticancerdrugs shou]d be followed iu compliance with the standard operating procedures (SOPs) of the study site. Refer to ,th e pharmacy instrnction for detailed infonuation about preparation and adminjstration of DS-820la.

5.2.4. Administration

TI1e st u dy dmg w ill be administered every 3 weeks at the 6.4 mg/kg. The initial dose of DS-820la will be infused intravenously into each subject for approximately 90 minutes. If there is no infusion-rela ted reaction after the initial dose, the se-eond and thereafter dose of DS-820la will be infused intravenously into each subject for approximately 30 minutes. The subject's weight at screening (baseline) will be used to calculate the initial dose. If dming the course of the treatment, the subject's weigl1tchanges by more than l0% of the baseline \veigh t, the subject's dose will be recalculated based on the subject's updated weight_

5.2.5. Storage-

Dmg supplies must be stored in a secure, limited access storage area uuder the storage conditions listed below:

- Stored at 2°c to 8°C (protected from light)

If storage conditions are not maintained per specifie<l req uirement,sthe sponsor or contract research organization (CRO) should be contacted.

5.2.6. Drug AccountabUJty

· w hen a study dmg shipment is received, the investigator or designee will check the amount and condition of the dmg check tl1e approp riateness of the label , drug expiration date and sign the Receipt of Shipment Fonn provided by sponsor. Tl:1e Receipt of Shipment Form should be signed and the original Fonn will be retained at thesite< In addit io11, th e inv estigator or designee shall contact the sponsor as soon as possible if ther-e is a problem with the shipment.

Dmg Acco untability Record will be provided for thestudy dn1g. The record must bekept current and sho uld co n tain the dates and quantities of study drug received, subject ' s information (thesite subject identifier and the subject nw11ber) for whom the study drng was d ispe nsed, the drng number, the date and quantity of srudy drug dispensed and remaining as well as the initials or seal of the dispenser.

At the end of the stu dy. as per local la ws and/or directed by Sponsor. all unused DS-8201a will be returned or destroyed as per local laws or s i te policy and only after the study monito r has completed a final inventory. As applicab le, the study site must file a copy of the appropriate institution pobcy witlrin their investigatorsitefile and provide a copy to the Sponsor. Please see pharmacy manual for details.

All investigationaJ product inventory forms must be made available for inspection by a Sponsor authorized representative or designee and regulatoryagency inspectors.

5.3. Coutt·ol Tr·eatment

Not Applicable.

5.4. Dose Modifications for r\llanaging Adverse Events

The investigator will evaluate which toxicities are attributable to DS-820Ia and adjust the do se of DS-820la as recommended below. All dosemodifications (interrn ption , reduction and/or discontinuation) should be based on the worst preceding toxicity (Common Tenninology C1iteria for Adverse Events [CTCAE] version 5.0). Specific criteria for intem 1ption, reinitiating, dose reduction and/or discontinuation ofDS-820la are listed in Section 5.4. All intem1ptionsor modifications must be recorded on the case report fo1111 (CRF). Appropriate clinical experts should be consulted as deemed necessary.

For Grade 3 or Grade 4 events, mouit01ing (including local laboratory tests when approp1iate) sho uld be perfo an ed at intervals. no greater than 7 d ays until AE is detenn..ined to be resolviug or subject is discontinued at end of treatment.

Prophylactic or supportive treatment for expected toxicities, including management of study-d:rng induced adverse events will be as per the treating physician's discretion and institutjonal guidelines.

Dose Reduction Guidelines:

NOTE: There ·will be no dose modifications for Giade **1** or Grade 2 AEs unless specified. in Tabl.e 5.2 .

Two dose reductions will be pennitted. The adjustment for a reduced dosing of DS-8201a is as shown in Table 5.1.

Table 5.1: Dose **R eduction Levels** of **DS-820la**

Starting Dost'	**n ose Lcvt'l - I**	**D ost' Lt>ve] - 2**
6.4 mg/kg	5.4 mg/kg	4.4 mg/kg

Once the dose of DS-820la has been1·educed because of toxicity, all subsequeut cycles should be administered at that lower dose level tmless fhrther dose reduction is requ ired. More than 2 dose reductio ns arenot aUowed and the subjectwill be withdrawu from the stud y treatment if further toxicity meeting the requirement for dose red uction occurs. DS-820Ia dose increases are not aJlowed in the study.

Dose Interruption mu:! Modificntion/Toxicity }J"ana'lement G11ideli11es :

A dose can bedelayedfor up t.o 28 days (49 days from the last inthsfon date) from the planned date of administration. If a subject is assessed as requiring a dose delay of longer th.an 28 days, the subject will be withdnn:vn from the study.

Treaflnent cycles for a su bject fo,r, hom DS-8201a dos ing is temporarily withl1ld for any reason may have fhnire cycles scheduled based on the date oft:he last DS-820la dose.

All confinned or suspectedSARS-CoV-2infection events must be recordedin the eCRF. Please refer to Appendix 17.5 for additional infom1ation on dose modification.

Table 5.2: Dose or schedule modification for DS-8201a

Won;t toxklty CTCA.E v .O Grade (unless otberwi\e specified)	**Do e 01· schedule modi1kathm for DS-820la**
l\"o toxkily	1aintain dose and schedule
lnfRsio a-Rehded Reaclion	
Grade I (Mild u-ansieIII reaction ; infusion intem iption not indica ted; intervention not indicated)	• If i1ifbsioti related reactio11(sud1as fevet and ch.i lls. 'll.tith arnl V.'ithour nm1s.ealvo nu ting.pain. headache. dizziness. dyspnea. l1ypote11s io11) is observed **during** administration, the iufa.sion rate should be reduced by *5 -b* and subjects should be closely monitored. • Ifno other reactious appear, the su'Mequen t infusion rate could be resumedat the initial planued rate.
Grade 2 (Therapy or infusion interruption indicated but respouds promptly to symptomatic rream.1.e.nt (eg auti histamwes. NSAIDs. narcotics. IV fluids}; prophylactic medications indicated for S24 hrs)	• Admin:istration ofDS-820la should be intem1pted and sytnptomatic treatment sta.ite d (eg. antihistamines. NSAIDs. narcotics. IV fluids). • If the even! resolves 01·imp roves to grade, 1 inftlsion can be re-sla1100 al a 50% reduced infusion rate. • Subsequentadministrations should be comh1ctedat the reduced rnle.
Grade 3 01· 4 (Prolo_nged 01· Jife-thl.'ea1e11i:11gcon quenees._ m·gelll int erve1 11ionindicated)	• Adm.inistrationof DS-820Ia should be discontinued immediately and permanently. • Ur[lent intetYeution indicated. Anti]i.istamines, steroids. epinepluine. broacilodilatol'$. vasopre!.sors. intravenotl.!, flu id therapy. oxygen inhalation etc.. shouldbe adn.lin.istered
Hematologic Toddty	
1'"°t'111ropbjJCo uot Den ·ensed aod/or Wh ite·Blood CeJJ Co uu(De cr ea sed	
Grade 3	Delay dose until resolved to:SGrade 2. then maiintain dose
Grade4	Delay dose until resolved to *5.*Grade 2: • Redm:e dose I level
Febrile Nemropenia (absolute nentrophil count <1 *x.* $10^9$1L, feyer >38.3°C or a !.UStained tempernlnre of;:::38 ° C for more than one bour	Delay dose until resolved: • Reduce dose by 1 level
Lympboc)'ie CotmtDeneased•	
Grade I to Grade 3 lymphopenia	No dose modification
Grade 4 (<0.2 .,. 109/L)	Delay dose until resolved to Grade 2: • If resolved in 14 days from day of onset. maintaill dose • Ifr esolved in >I4 days from dayofonset. reduce dose 1 level

Table 5.2: Dose or schedule modification for DS-8201a (Continued)

Worst toxicity CTCAE v.O Grade (unless otherwise specified)	Dose or schedule modification for DS-8201a
Anemia	
Grade 3 (Hemoglobin (Hb) <8.0 g/dL); transfusion indicated	Delay dose until resolved to ≤ Grade 2, then maintain dose
Grade 4 Life threatening consequences; urgent intervention indicated	Delay dose until resolved to Grade 2, then reduce dose level
Platelet Count Decreased	
Grade 3 (platelets < 50 to 25 x 10^9/L)	Delay dose until resolved to ≤ Grade 1: • If resolved in ≤ 7 days from day of onset, maintain dose • If resolved in > 7 days from day of onset, reduce dose level
Grade 4 (platelets <25 x 10^9/L)	Delay dose until resolved to Grade 1, then reduce dose level
Cardiac- Toxicity	
Symptomatic congestive heart failure (CHF)	Discontinue subject from study treatment
Decrease in LVEF 10% to 20% (absolute value) but LVEF ≥ 45%	Continue treatment with DS-8201a
LVEF 40% to ≤45% and decrease ≥ 10% (absolute value) from baseline	Continue treatment with DS-8201a Repeat LVEF assessment within 3 weeks
LVEF 40% to 5% and decrease is 10% to 20% (absolute value) from baseline	Interrupt DS-8201a dosing Repeat LVEF assessment within 3 weeks. If LVEF has not recovered to within 10% (absolute value) from baseline, discontinue subject from study treatment If LVEF recovers to within 10% from baseline, resume study drug treatment
LVEF <40% or >20% (absolute value) drop from baseline	Interrupt DS-8201a dosing Repeat LVEF assessment within 3 weeks. If LVEF < 40% or > 20% drop from baseline is confirmed, discontinue subject from study treatment
Electrocardiogram QT prolonged	
Grade 3 (QTc> 500 ms on 2 separate ECGs)	Delay dose until resolved to grade 1 (collected QTc ≤ 480 ms), determine if another medication the subject was taking may be responsible and can be adjusted or if there are any changes in serum electrolytes that can be corrected, then if attributed to DS-8201a, reduce dose level
Grade 4 (QTc > 500 or > 60 ms change from baseline and Torsade de pointes or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia)	Discontinue subject from study treatment

Table 5.2: Dose or schedule modification for DS-8201a (Continued)

Wont toxklty CTCAE v5.0 Grade (unless otberwbe specllll'd)	**Do\e 01·schedule modificatf● for DS-820la**
Troponin	
Grade I (Levels above the upper limit of nonnal and below the level of myocardial infarction as defined by the manufacturer)	If troponin 1evels al'e abo,·e the lrpper limitof nomial at baseline aud below the level of mYQcardial infarction as defined by tl1e manufacturer (CTCAE Grade I) at baseline. no repeat testing is required after the first end of iu.lils ion 3-hour lrnponin test if the tropouin level is not Grade 3. For new diagnosed Grade l. repeat tropouin testi.1111 at *3* ± 1 hours(~ *6* hot post-infilsion) after initial troponi.J1 tes t. If repeat troponin level at 3 ± I hours (~ *6* hours post-infaisio n) rises significantly per institutional guidelines. • Perfon11ECG il1 t1ipl icate • Repeat trop o1rin testing **at** 6 ± 1 l1our (-9 hours post-iufosion) !'lfter initial troponin test • Follow institutional guid elinesfor maoage111ent ofdetectable uopollin tes ting. Ifrepeat Lroponin leve l at 3 ± 1 hours (6 hours post-infusion) does not risesignificantly per instimtional guidelines, • Repeat troponiu testing **at** 6 ±] hours (~9 hours pos1-i11fu ion) or at 24 ± 2 hours (-27 hours post-infm;io)uatler initial troponiu test. • Contin ue tre,1tment with DS-8201a.
Grade 3 (Levels co11S.isteot ·with myocardial infarction as defined by the manufacnlle1')	Perfom1ECG in triplicate Repeartroponin testing at *6* ± 1 hours (~9 hours post-infusion) and 12 ± 1 hours, (- 15 hours post-infitsion) after initial troponin test. Follow insrinnional guiddines for management of detectable troponin testing. lf acute myocardial infarctionconfirmed,discontinue subject from smdy tilerapy. Othernise, delay dose1mtiJ resolved to Grade 1; • If resolved in 5.7 da.ys from day of onset. maintain dose • If resof\·ed in > 7 days fromday of onset, reduce dose I level

Table 5.2: Dose or schedule modification for DS-8201a(Continued)

Won,t toxk lty CTCA.E v .O Grade (unl es s othe r wi w 11ec it le d)	Do e 01· ch edule modifk atl0n for DS-8201a
Puhnou:iu-yToxlcll)•	If a subject develops radiographic changes polentia.Uy consisten t with ILD/pnumonliis or develops an acute onset of new or worsening pulmouary 01 other related signs/s} hptoms such as dyspnea.cough or fever. mle out lLD/pneumonitis. If tl1e AE is confinned to ha,·e an etiology other than ILD/pueumonlis. follo\v the m,magement guidance outJined in the "Other Non-Laborntocy Adverse Eveuls" in tl1e dose modification section below. If t11e A E is :mspectedto be ILD/pneumonitis.treatment with study dmg sbould be intemrpted pending: further evaluations. Evaluations should include: • High resolutionCI • Puhnonologist consultation (Infectious Disease consultation as clinically indicated) • Blood culnue and CBC. Other blood tests could be considered as needed • Consider bronchoscopy and bronchoalveolai· lavage if clinicaJly indicated and feasible • Pu.lmonary fum::tiou tests and pulse oxime1ry (SpO_2) • Arterial blood11ases ifd inica11y indicated • One blood wmple collection for PK analysis as soou as TLD/pne umonitisis suspec ted if feasible. Other te.sts ,could be considere d, as needed. If the AE is confirmed to be IIn /pnemnonit,isfollow the ILD/pneumollitis managemern guidanceas outlined beJo w. AJJ events of ILD/pmunouitisregardless of severity or seriousness wilJ be follo,ved lUiltil resolution including afte r dmg discollti uuaJi·ol
Gn 1d e 1	The administration of DS-820la must be intemipted for any Il.D/pnumollitisevents regardless of grade. • foDitor and closely follow-up in 2 to 7 da:ys for onset of clinical symptoms and pulse oximetry. • Consider follow-up imaging W 1-2 weeks (o r as clinically indicated). • Consider starting systemic steroids (e., . 11t leasl 0.5 mgJk g/cbty prednisone or equivalent) until improvement. followed by gmdu.al taper ovel' at le st 4 weeks. • lf wol'sening of diagnostic observations des-pile initiatioll of c011ico.s reroids. tben follow Grade 2 guideli1 lse For Grade I events. DS-820la can be res1aned only if the event is fiaUy resolved to Grade 0: • Ifresol,•ed in 28 days from day of onset maintain dose • If resolved in > 28 days tlom day of onset. reduce dose I lewl However. if the event Grade 1 ILD/pnumouitsi occurs beyond cycle day 22 and has not. t'esolved \Vi.thin 49 days from 1.he last. infilSion the dillg should be disconti11ned. • Jf subjec 1 is asymptomatic. theu- ubject should still be oonsMered as Grade I even if stel'oidtreatmell is given

Table 5.2: Dose or schedulemodification fo1· DS-820la (Continued)

Wont toxklty CTCAE v5.0 Grade (nnless otberwbe Sl)ecified)	**Do e 01· schedulemodifirathrn for DS-820la**
G11tdl" 2:	Pennanently dis.con tinue subject from study treatment. • Promptly start and treat with systemic r;teroids {e.g:.. at le,l.st 1 mg/kg/day predniso11.e or equivalent) for at least l4 day'.i or tmtil complete resolutiouof clinical aud chest CT fimh gs. then followed by a 1tradual taper over at least 4 weeks. • Monilor symptoms dosely. • Re-imageas clinically indicated. • If worseningor no improvement in clinical or diagumtic observationsin *5* days. • Consider increasingdose of stewids (e.g.. 2 m,glkg/day predni.sone or equivalent) and administration may be s·witched lo intravenous (e.g. metl1ylprednisJ0one). • Re-consideradditioottl work-up for alternative etiologiesas desc-ribe d above. • Esca]ate care a:;, clinically indicated.
Grade 3 and 4	Pemlalleotly discontinue subject from study treatment. ▪ Hospitalization required. • Promptly initiate empiric high-dose methylprednisoloneJV tre-atm en t (e.g.. 500-100 0 mg/day for 3 days). followed by at least l.O m g/kg/day of prednisone (or equivalent) for at least 14 days or until complete resolutionof clinical aud chest CT findings. then followed by a gradual raper onr at least 4 weeks. • **R** •imlge as cli nk-{llly indi-ati:d, • If s ti1 1 no improvement within 3 to *5* WI) 'S, • Re-consider additional work-up for altema1ive etiologies as described above. • Consider other immllllo-suppressants and/or treat **per** local practice.
Ocular	
Grade 3	Delay dose until resoh-erl to Grade I: • If resolved in *S* 7 days from 00y of onset. maiut<li0 dose • If resolved in> 7 days from dayof ouset. reduce dose I level
Grade 4	Di5continue subject from study treatment
Bl ood<'r ('atlnlne lllCl't'ased	
Grade 3 (>3.0 lo 6.0 xlJLN)	Delay dose until resolved to Grade 2 or baseline. then reducedose 1 le\·el
Grade 4 (><>.0 x ULN)	Discontinue subject from study treatment

Table 5.2: Dose or schedule modification for DS-8201a (Continued)

Worst toxicity CTCAE v5.0 Grade (unless otherwise specified)	Dose or schedule modification for DS-8201a
Hepatic Toxicity	
Aspartate aminotransferase (AST) or Alanine aminotransferase (ALT) with simultaneous Total bilirubin (TBL)	
AST/ALT ≥3.0 x ULN with simultaneous TBL ≥2.0 x ULN	Delay study medication until drug-induced liver injury can be ruled out. If drug-induced liver injury is ruled out, the subject should be treated accordingly, and resumption of study drug may occur after discussion between the Investigator and Sponsor. If drug-induced liver injury cannot be ruled out from diagnostic workup, permanently discontinue study treatment. Monitor AST/ALT and TBL twice weekly until resolution or return to baseline.
AST or ALT	
Grade 2 (>3.0 to 5.0 x ULN if baseline was normal; >3.0 - 5.0 x baseline if baseline was abnormal)	No action for Grade 2 AST/ALT
Grade 3 (>5.0 to 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal) In subjects without liver metastases and subjects with liver metastases and baseline level ≤ 3 x ULN	Repeat testing within 3 days. Delay dose until resolved to ≤ Grade 1 if baseline was normal; ≤ 3 x ULN, otherwise delay dose until resolved to ≤ baseline. Then: • If resolved in ≤ 7 days from day of onset, maintain dose • If resolved in > 7 days from day of onset, reduce dose 1 level
Grade 3 (>5.0 to 20.0 x ULN if baseline was normal; >8.0 to 20.0 x baseline if baseline was abnormal) In subjects with liver metastases, if the baseline level was >3 x ULN	Repeat testing within 3 days. Delay dose until resolved to ≤ baseline level. Then: • If resolved in ≤ 3 days from day of onset, maintain dose • If resolved in >7 days from day of onset, reduce dose 1 level
Grade 4 (>20 ULN if baseline was normal; >20.0 x baseline if baseline was abnormal)	Discontinue subject from study treatment
TBL	
Grade 2 (>1.5 to 3.0 x ULN if baseline was normal; >1.5 - 3.0 x baseline if baseline was abnormal)	If no documented Gilbert's syndrome or liver metastases at baseline, delay dose until resolved to ≤ Grade 1: • If resolved in ≤ 7 days from day of onset, maintain dose • If resolved in > 7 days from day of onset, reduce dose 1 level If documented Gilbert's syndrome or liver metastases at baseline, continue study treatment

Table 5.2: Dose or schedule modification for DS-8201a (Continued)

Wont toxklty CTCA.E v .O Grade(unless otberwi\e 11ec U:led)	**Doi;;e 01 chedulemodi1kathm for DS-8201a**
Grade 3 (>3.0 to I0.0 ,. ULN if baselilile was normal: >3.0 to 10.0 x baselil-ie ifbaseline was abnonnal)	Ifno documented Gilbert's syndrome or liver metastases al baseline. repe<tt te s t in within 3 days. Delay dose until resolved to 5 Grade l: • If resol\'ed in 5 7 days from day of ouset reduce dose 1 le\'e) • If resolved in > 7 days from day of ons.el, discontinueDS-820 la If documented Gilbert"s syndrome or Jjver metastases at baseline. repeat testing within 3 days. Delay dose uutil resolved to 5 Grade 2: • If resol\·ed in 5 7 days from d.ly of ouset. reduce dose 1 level • If resol\·ed in > 7 days from dayof onset. dhcontinue DS-820 la
Grade 4 (>10.0 "- ULN if bac;eline was uonnal; >10.0 x ba,;eline if baseline was abnormal)	Discontinue subject from study tre.atmen t
Blood AJkalLoe Pho sphata se l nt t'eased	
Grade 3 (>5.0 to 20.0 x Ul.N ifbaseljJile was normal; >5.0 to 20.0 x baseline if baseline was abnonnal) or Grade 4 (>20.0 x ULN if baseline was normal: >20.0 x baseline if baselim: was abnormal)	No modification unless determined by the hivestigator to be clinically significant or life-lbreateuiug.
Gastrnlnte;i.1inal	
Nausea	
Grade 3	Delay dose \mtil resolved to Grade 1 • If resolved in 5 1 days from ooy of ouset. nu1intai11 do5e • If resolved in > 7 days from dayof onset, reduce dose 1 level
Diarrhoea/Colitis	
Grade 3	Delay do until resolved ro Grade I • If resolved in 3 days from day of onset. maintain dose • If resol\'ed in > 3 days from dayof onset, reduce dose I level
Grade4	Discontinuesubject from study treatment
Othe1· Laborator y Ad•terse Events	
Grade 3	Delay dose until reso, h-e d to Grade I or bas eline le vel: • Ifresolved in 5 7 days from day of ouset. m;uutai11 dose • If resolved in > 7 days from dayof onset. reduce dose 1 level
Grade 4	Discontinue subject from '>tudy tre.annen t

Table 5.2: Dose or schedule modification for DS-8201a (Continued)

Wont toxklty CTCA.E v .0 Grade (nnless otberwir,e specified)	Doi;e 01 · s chedule mod ik atl00 for DS-820la
Otbet oi1-Lab-01·atoryAdvei·se E\leuts	
Grade 3	Delay do:,e until resolved to:::Grade I or bilseline'. • Ifresolved in S 7 days fromday of onset. maintain dose • If resoJ!ved in 7 dayi, from dayof ow,et. reduce dose 1 level
Grade 4	Discontinue subjecl from smdy treatmenl

AE = adverse event. ALP = alkaline phosphil-tase. ALT = L-alanine aminotransferase. AST = L-aspartate aminotransferase, CT = computed tomography. CTCAE: Common Tecmi nology Criteria for Adverse Events, ECG= electrocardiognun. *ILD* = interstilitl.!l\mg disease, IV = intravenous. LVEF = left ventricular ejection fraction.. NSAIDs = nonsleroidal anti•inflilD1111atory drngs, QTc = corrected QT, TBL = total bi]irubin. ULN = upper Tuni1 of nonnaL
a. There will be no dose modifications for grade I to grade 3 !ymphopeuia.
All dose modifications should be based on the worst proceeding toxicity.

In additio,n investig ato rs ma y consider dose reductions or discontinuations of the study dmg according to the subject's conditionand after discussion with tbe Daiichi Sankyo's Medical Monitor or designee.

5.5. I\llet hod of Assessing Treatment Compliance

DS-820la will be administered rv only to su jec ts p ruti cipating in the sn1dy and under the s11pervisionof clinical study persom1 ·leat tbe study site. Therefore, treatment compliance will be guaranteed as long as tbe subject attends each visit for administration of the study treatment Start and stop dare/time of injection, amount of drug administered, and reason for cha11ge or interruption (if applicable) must be recorded in medical record by clinical stu<ly personnel. TI1ese data wiJl be recorded in the electronic case report fonn (eCRF).

5.6. Prior and Concomitant Medications

Medications used from the time the subject signs the informed consent form for study participation tbe F/U 40 days visit(± 7 clays) after the last achninjstrationof DS-820la will be recor ded . Prophylactic treatment for the study treatment and all concomitant medications will be recorded in the eCRF.

With the exception of medications that are tmder investigation in the study (e.g. standard of care. comparators, or combinahon Hiernpies. tbe following medications and producls will be prohibited dming the treatmen t period. The Sponsor must be notified if a subject receives ru1y of these duriug tl1e study. :

I. Other anticancer therapy, including cytotoxic, targeted agents, imnmnotherapy, antibody. retinoid , or anti-cancer honnonal tre.atment [concuiTent use ofho1mones for non can cer-re la ted conditions (e.g. insulin for diabetes and honnone replacement therapy) is acceptable].

2. Other investigational therapeutic agents.

3. Radiotherapy (except for pallfative radiation to known metastatic s ites as long as it does notaffect assessment of response and it does not intenupt tre.atmen t for more than the maximum time specified in dose modification sec tion).
4. Radiotherapy to the thorax.
5. Concomitant use of chronic systemic (IV or oral) cmiicos teroids or other imnmnosuppressive medications except for managing adverse events; (Inhaled steroids or intra a1ticular steroid injections a.re permitted in this study.) Subjects with bronchopulmonary disorders who require intermittent us e of bronchodilators (such as albuterol) will not be excluded from th is study.
6. Concomitant treatment with ch loroquine or hydroxychloroquiue is not allowed during the study t>eatment. Refer to appendix 17.5 for fut1her details.

Pea-mlttedThera1>les/Products

L Hematopoietic growth factor may be used for prophylaxis or treatment based on the clinical judgment of the investigator.

2. Concomitant use of dietary supplements, medications not prescribed by the h1Ve st iga tor. and alternative/complementary treatments is discouraged. but not prohibited.
3. Prophylactic or supportive tre<'ltrneut of study-drng induced AE will beothenYise as per investigator's discretion and the institutional guidelines.
4. Based on the CUITently available clinical safety data. it is recommended that subjects receive prophylactic anti-emetic agents p1ior to infusion of DS820la and on subsequent days. Antiernetics such as 5-hydroxytryptamine receptor (5-HT3) antagonists or Neurokinin-1 (NKl) receptor antagonist.sand/or ste roids (e.g. dexamethasone) shouldbe considered and administered in accordance with the prescribing informatiou or .inst i tutional guidelines

Restricted Products

1. Use of e-cigarett es and vaping is strongly discouraged but not prohibited

5.7. Subject \\ 1ithdrawal/Discontinuation

5.7.1. Reasons for Disconfinuatim of Study Treatment

Subjectsmay be withdrawn from snidly treatment after signing the infonned consent for the following reasons:

- Progressive disease per RECIST version I. I ass essed by the investiga tm·;
- Clinical progression (definitive clinical signs of diseaseprogression, but a recent radio graphic assessment did not meet the criteria for Progressive Disease according to RECIST version1.I);

- Adverse event:
- Withdrawal of conse nt by su ject;
- Phys ician Decision ;
- Death:
- Pregnancy;
- Study term.mated by Sponsor ;
- Lost to FfU:
- Others , specify.

All subjects who are withdrawn from the study treatment should complete protocol-specified withdrawal procedtires (Section 5.7.3) and FIU procedures (Section 6.6).

Record the reason for any subje-Ct who discontinues study treatment. Discontinued subjects \\Jill be followed for survival, either through direct contacts or by collecting public records (eg, death certificates) as allowed by local laws.

5.7.2. Reasons fo1• Discontinuation of Study P.ar·ticipation

Subjects may be withdrawn from smd.y after snidy treatment for tl1e following recasons:

- Subject wit11drawsconsent to pa11icipate in study procedures;
- Subject dies;
- Study is tenninated by the sponsor:
- Subject is lost to F/U;
- Others, specify.

5.7.3. '\\'ithdrawal Procedures

If a subject is withdrawn from the study, the investigator will complete and rep01t the obse1vations as thoroughly as possible up to the date of witbdrawa] induding the date of the last treatment and the reason for withdrawal.

If the subject is withdrawndue to au adverse event, the investigatorwill follow the subjec.t until the adverse event has resolved or stab ilized , pos.t ca ncer treatment, or lost to F1U.

All subjects who are withdrawll from the sn1dyshould complete protocol-specified withdrawal procedures. Protocol-specified withdrawal procedures will be obtained dming the end of treatment visit (+ 7 days)and the F/U 40 days visit (+ 7 days) conductedafter the last administration ofDS-8201a (Section 6.5 and Section 6.6).

5.7.4. Subject Replacement

Subjects that have been emolled and administered sru.dy medication will not be replaced. It is allowable to replace a subject that was enrolled but was not administered any study medication.

5.7.5. Subject Re-screening Procedures

Re-screening is peanitted for any subject who failedto meet the eligibility crite1ia in the initial screening. The limit of re-screening is 1 time. The site subject identifier and the subject number must remain the same at the time of re-screening. The initial screening in.fonnation and tbe reason why the subject was ineligible for the initial evaluation wiU be recorded in the Screening Log. No data from the initial evaluationwill be entered into the clinical database for a subject who is i-escreened.

6. STUDY PROCEDURES

A sn1dyvisit schedule in tabular fonu:at is provided in Section 18. Obtain a signed and dated ICF before any st1_dy-re1ared procedures or assessments are conducted. A separate tissue screening ICF may be used to o btain consent to send the sample to the central laboratory.

After obtaining informed consen,tthe investigator or designee assigna site subject identifier.

hlfonned c-0nseut for pllannacogenomics study \ltill beobtained separately.

6.1. Tissue Screening

To detennine eligibility, subjects must meet tumor biomarker criteria.

Note: A separate tissue screening ICF may be used to obtain consent to send the sample to the central laboratory. Subjects may continue ou prior therapy while tissue testing takes place.

Please refer to the sh1dy laboratory manual for required huuor sample specifications and shipping instmctions

The fo1lowingprocedures will beconducted:

- Obtain a signed and dated written consent from the subject to collect tiss.ue and/or pe1fonu a biopsy as needed.
- Obtain adequate archival or recent tumor tissue sample for HER2 testing. Approximtely 1Oslides or adequate paraffin-embeddedtissue blocksof fonnalin-fixed tissue specimens can be submitted for this analysis.
- · Send the sample to the Central Laboratory to confirm HER2 status
- If a tumor biopsy is needed, record any SAEs directly rela ted to tissue screening procedure (ie, tumor biopsy).
- For su bject s who sig n only the Informed Consent Fmm for tissue scree uin g, repo11 only se1i ous adverse events (SAEs) directly related to tissue screening procedure {ie, tumor biopsy). Unless documentation of other AEs is required by local law. only SAEs directly related to tumor biopsy will be recorded during tissue scree nin g.

6.2. Screening

Obtain a signed and dated ICF before any study-re lated procedures or assessments are conducted. After eligibility is met, the subject will be registered to lXRS as eligibleand assigned to the coho1t. Subject who is ineligible after obtaining ICF for sh 1dy entry should also be registered as ineligible in tbeIXRS.

The fo11owing activities and/or assessments will be perfonned dutin g the screening _period:

- Obtain fresh nimo r biopsy specimen fi.'Om a subject. Tum or tiss ue will I>e sent to the central laboratory for an explorator.y b i omarkeranalysis. Fresh biopsy is

not needed if a sample that was obtained after the most rec ent anti-cancer therapy is a]ready available. Further details will be provided in the laboratory manual.

Within 28 days before emollment (study treatment)

- Perfo1m a HIV antibody test. It is testedas required by local regulations or IRB/ECs.
- Perform bepafjtis B surface antigen test, atid hepatitis C antibody test.
- Ophthalmologic assessments. The assessDnents will include visual acuity testing, slit lamp examination, and fimdoscopy.
- Perform an ECHO or MUGA (note: the same test must be used for t,he subject throughout the study).
- Perfonn tumor assessment by computed tomograph y (CT) or magnetic resonance imaging (l\llRI) sc ans of the chest, abdomen, pe1vis, and any other sites of disease. A CT or 1'00 of the brain is to be included for all subjects.

  NOTE: To assess objective response or foture progression, it is necessaryto estimate the overall tmnor burden at baseline and use it as comparator for subsequent measurement. Therefore, all lesions (target a11d non-target) have to be assessed at Screening according to RECIST version 1.1 (Section 17.3).

T11e fo1lowing activities and/or assessmentswill be perfonned during the screening period within 14 days before enrollment (st11dy treatment) except as indicated:

- Obtarn demographics (eg, l1irth <fate, sex. race, etlmicity,) medical and surgical hi.story, including all previous, now resolved, sig:u.ifi c.ant medical conditions, date of diagno,sis extent of disease, disease staging, Primary tmnor site (rectum, sigmo id, descending, transverse ascending, cecmu), previous cancer therapies (including p1ior radiation therapy), histotical RAS (KRAS/ ueuroblastoma RAS viral oncogene homolog) status, *BR.AF* status, microsatell.ite instability stanJS, his torical HER2 stanis and oncology surgical history.
- Perform a complete physical examination (ee Section 9.11) incJuding weight and. height.
- Assess i\Es throughout the screening pe1iod (from the time the subject signed the ICFfor study entry).
- Record concomitant medications (from the time the subject signed the. ICF)
- Obtain vital signs (systolic and diastolic blood pressure, pulse rate, body temperature) and peripheral oxygen saturation (SpO 2).
- Assess functional status using t11e ECOG PS Scale (Section 17.2).
- Obtain blood samples for hematologyand. blood chemistry tests (includes caJculated creatinine clearance. See Section 17.1), coagulariou(prothrombin time and activated partial throruboplastin time), troponins (preferably high-sensitivity troponin-T) and HER2ECD. TI1e test used to test troponin should

remain the same throughout tJ1e cour se of a su bject's time on study. An additional sample should besubmitted for central lab troponin-T testing.

- Peif orm urin alysi s te st
- Perfo rm a 12-lead ECG in triplicate. See Section 11.4.3.4 for conected QTc. Average of the triplicates should bechecked for screening.

  •: ECGs will be tak en in close succession a few minutes apart, after the subject has been in a supine/semi-recumbtequsition.
- Revi ew inc lusion /exclus io u crit eria.

With in 72 hours prior to enrollment (sh1dytreatment)

- Obtain a sernm or urinesample for pregnancy testing in women of childbearing potential. Test must be confirmed within 72 hours prior to enrollment (studv treatment). For postmenopausal subj.ects (no childbearing potential, as indicated by an elapse of at least 12 months after the last menstrnation) or subjects \Yho have no possibility of pregnancy due to sterilization surgery , etc., no pregnancy test w ill be requi red. Su bjects who have been amenoTtheic for 12 months or longer for medical ieasons other thansterilization surgery (eg, effect of medica tion) \vilJ be rega rded as women of child-bea ring potenti al and required to undergo the pregnancy test. A positive urine pregnancywill be confirmed using blood test.

6.3. Randomization

Not applicab le.

The su bjects ·who consented to sn1dyentry should be registered to IXRS.

6.4. Tr·eatm e n t Period

Treatment will be sta1ed as soon as a subject is registered to IXRS.

6.4.1. Cycle 1 to Cyde 4 andSubsequent Cycles

Treatment and proceduresperf01111ed on Day 1 of Cyde 1 and beyond are spec ified in Section I8. Procedures are to be perfo nu ed w ithin 3 day s of the Day 1 visit of each cycle unless otherwise specified.

Physic.a] examination, weight. ECOG PS assessme, nt 12-lead ECG. hematology. blood chemis try, and vital signs (including SpOz) evaluation s do **not** need to be repeated at the Cyclel , Day I visit if per fo nned within 3 <lays before the first do se of sh1dy drug.

Before Dosing:

- Record concomitant medications and AEs at every visit. Safety will be monitored by assessment as well as by collection of the AEs at evety visit. For detaisl 011AE collectiou and reporting, referto Section 9.4.
- Obtain a blood sample for phanu acogenetic assessment on Day 1 of Cycle I. (This sample is not required for study panicipationand w·ill be collected from

subjects \.Vho have provided consent by signing the phanuacogenetics sample banking consentfonn.)

- Blood samples for ctDNA analysis wiU be collected before treatment on Day I of Cycle 1 and Cycle 4.
- Physical examination (Sec tion 9.11) will be pe1fon ned on the scheduled day even if study treatment is being withheld. More frequent examinations may be perfonned at the discretion of tbe investigatorand if medkally indicated. Weight is recorded.
- Ophthalm ologic assessments to include visual acuity testing, slit lamp examination and fondoscopy will be perfonned at Da y 1 of Cycle 2 (within 3 days before administration) and every 4 cycles(± 7 days) thereafter (eg, Day 1 Cyc1es 2, 6, 10, 14...).
- Vital signs (systolic and diastolic blood pressure, pulse rate. body temperature) and SpO_2 wiU be perfonned as per the Schedule of Events. !\fore frequent examinationsmay be perfonned at the discretion of the inve stigator and if medically indicated.
- ECOG PS wiH be assessed as per the Schedule of Events.
- Blood samples for hematology and blood chemistry assessments will be collected as pet: the Schedule of Events. Refer to Section 9.8 for a list of parameters to be evaluated!.
- Tripl icate 12-lead ECG will be perfonned at every cycle. ECGs should be perfonued before PK blood draws at respective time points. ECGs will be taken in close succession, a few minutes apart. after the subject has been in a supine/semi-recmu bent position_
- Perform an ECHO or fvfUGA scan assessment (note: the same test must be used for the subject throughout the study) every 4 cycles(± 7 day) starting with Cycle 5 (eg, Cycles 5, 9, 13...).
- Blood samples for I-IER2ECD assessment will be collected on Cycle 3 Da y 1 and eve.ry other cycle thereafter (eg, Cycle& 3, 5, 7, 9...). A ponion of this blood sample from each subject who provides consent will be used for future central lab analysis for S.>\RS-CoV-2 testing at Cycle 5 Day 1 aud every 4 cycles thereafter (Cycles 5, 9, 13, etc).
- Obtain a sen un or urine sam ple for p1egnancy testing in women of childbearing potential. Test must be confirmed within 72 hours prior to drug achuh ustr ation. A positivemine pregnancy will be confirmed using b]ood test.

- 8 to O hours of infosion

- Blood samples for PK assessments will be obtained before infusion (- 8 to 0 hours) on Day 1 of each cycle through Cy:cle 4; then at Day 1 of Cycle 6.
- Blood samples for ADA will be obtained before infusion (- 8 to 0 hours) on Day 1 ofCyde I, 2 and **4,** and then every *4* cycles.

Dosing and Post Infusion Assessments:

- Administer DS-8201a IV infusion approximately 90 minutes for the initial dose and, if 110 infusion related reaction after the initial dose, iufuse subsequeut doses over approximately 30 minutes. Record start and stop times. DS-820la is to be administered every 3 weeks ± 3 days.
- Collect blood samples within 15 miuutes after end of infusion (EOD for PK analysis for on Day 1 of each cycle thrnugbCycle 4; tbeu at Day 1 of Cycle 6.
- Obtain blood sample for PK assessments at die following time points
  - Cycle 1 Day 1
    - 4 hours after the stari of cl.mg a dministration (± 15 minutes)
    - 7 hours after the sta11of dmg administration(± 2 hours)
  - Cycle 1 Day 8 (± 1 day) and Day **15** (± 1 day)
  - Cycle 3 Day **l:**
    - 4 hours after the start of dmg administration(± 15 minutes)
    - 7 hours after the start of dmg adminitsration(± 2 bours)
  - If the scheduJe on Day 1 of Cycles 2 is delayed for 3 days or more, or if the subject cannot continue onto tl1e ne:i-..1 cycle, PK blood sample will be co llecte d on Day 22 of Cycle 1 as per the Schedule of Event
- Vita] signs (systolic and diastolic blood pressure, pu]se rate. body temperature and Sp02) w i ll be pe1fonne.d as per the Schedule of Eveu.ts. More .frequent examinations may be performed at the discretio n of the investigator and :if me<licaUy indicated.
  - Cycle 1 Day 8 (± 1 day) and Day 15 (± 1 day)
- Collect blood samples for troponin (preferably high-sensitivity troponin-T) 2 to 3 hours after end of infusion. The test used to test troponin should remain the same du-oughout the course of a su ject's time on study. Au additional sample should be submitted for centra] lab troponiu-T testing.
  - If troponin levels are consistent with myocardial infarction as defined according to manufacturer (C TCAE Grade 3), perfo1m ECG test in g in triplicate., repeat troponin testing 6 ±1 hours (~9 holuss post-infb s ion) and 12 ±I hours (- 15 hours post-infusion) after initial troponin test was drawn, and follow institutional guidelines.
  - If troponin levels are above the upper limit of normal and below the level of myocardial infarction as defined by the mmmfacturer (CTCAE Grade 1), repeat troponin testing at 3 ±I hours (~ 6 hours post-infusion) after initial troponin test was drnwn.

    If repeat troponin level at 3 ± 1 hours (~6 hours post-infusion) rises significantJy per insti tu tiona l guidelines, pe1form ECG testing in triplicate, and repeat tropouin testing at 6 ±1 hours (~9 hours post-in.fusion) and fo11ow institutionalguidelines.

If repeat trnpouin level does not rise significantly per institutional guideilnes, repeat troponin testing aJ 6 ±1 hours (~9 hotus post-infusion)or at 24 ±2 hours (-27 hours post-infusion) after initial troponin test.

If troponin levels are above the upper limit of nmmal at baseline and below the level of myocardial infa rction as defined by the manufacturer (CTCAE G rade I), no repeat testjng is required after the first EOI 3-hour troponin test if the tropouiu level is not Grade 3.

- Blood samples for hematology and blood chemistry assess ments **will** be collected at Cycle l Day 8 (± 1 day) and Day 15 (± 1 day) as per the Schedule of Events . Refer to Section 9.8 for a list of panuneters to be eval uate-cl.

6.4 .2 . Every 6 \\'eeks (:I: 7 d.ay s)

- Tumor assessments, based on sites of disease identified at. Screening and any ad ditional newly suspectecil s ites of progressive disease, will be conducted every 6 weeks (± 7 days) from Cycle I Day I, independen t of treatment cycle. CT or MRI scans of the suspected sites of disease in the chest, abdomen and pelvis are mandatory. Compute1ized tomography ancVor NlRI (spiral CT or MRI with ::=;5 ıuuuı cuts) of che.st, abdomen, and pelvis should be used for tumor assessment unless another modality of disease asse-ssmen t i s n ecessa ry for th e lesions. The same assessment modality should be used throughout the sn1dy for all assessments for each subject unless prior approval is obtained from sponsor or its designee. Unscheduled nuuor assessments may be perfo1med if progression is suspected.

- A CT or MRI of the brain .!is mandatory for all subjects included witll baseline stable brain metastases. S111bjects without brain metastases do not need additional brain scans for tumor assessment unless clinical]y indicated.

Imagingresults will be reviewedby an independent radiologic facility. Copies of CT or Iv1Rl im a ges s hould be provided after the images are takeu.

6.4.3. Fresh Tumo1· Biop sy Durin g Treatment

Obtaiu fresh nimor biopsy specimen f rom a subject at day 43 (± 7 days) if available_ Tumor tissue will be sent to tl1e central laboratory for an exploratory biomarker analysis. Further details will be provided in the laboratory manual. If the tumor is not taken. document the re.asou why the fresh tumor sample is unavailable.

6.4.4. Interstitial Lung Disease/Pneumonitis

For suspected ILD/pneumo nitis, trnatment with study drugshould be intem1pted pending further evaluations.

Eva]uatinos should incJude:

High resolution CT

Pulmonologist con sultation (Infect ious Disease consultation as clinica11y ind i cated)

- B1ood cult ur e and CBC . Other blood tes ts co uld be considered as needed

Consider bronchoscopy and bronc11oalveolar lavage if clinically indicated and feasible

Pulmonaryfunction tests and pulse oximetry (Sp02)

Arterial blood gases if clinically indicated

One blood sample c.ollectioofor **PK** analysis as soou as ILDipneumontis is suspected, if feasible.

Other tests could be considreed,as needed.

AH events of 11D/pnumonitis regardless of severity or seriousness will be followed until resolution including after dmg discontinuation.

6.5. End of Treatment

TI1e e nd of treatment (EOT) is defined as the date the investigator decides to discontinue shtdy treatment (+ 7 days). The following procedures will be performed as specified in the Schedule of Events. However, ifthe EOT assessments have been perfonned within 40 (+ 7) days of tl1eir last treatment t11ey can be considered to be the EOT data and thereis no need to repeat them., otherwise these assessments need to be repeated.

- Physical examination.
- Weight will be iecorded.
- Ophthalmologic assessments to include visual acuity testing, slit lamp examination, and fundoscopy.
- Vital signs (systolic and diasto1ic blood pressure, pulse rate, body temperature) and SpO2.
- ECOG PS.
- AEs and concomitant medications will be recorded.
- Blood samples for hematology and blood chemist!)' assessments will be collected. Refer to Section 9.8 for a lis.t of parameters to be evaluated.
- Blood sample for dDNA imalysis will be collec ted.
- Blood sample for HER2ECD a-sse.ssme nt. A portion of this blood sample fromeach subject who provides consent will be use.d for future central lab analysis for S.i\RS-CoV-2 testing.
- Triplicate 12-lead ECG.
- ECHO or MUGA (note: the same test must be used for the subject throughout the study).
- Senuu or urine sample for pregnancy testing in women of childbearing potential.
- Evaluations of tumor assessments should include all s ites of di sease identified at. screening and any other Jocationsif progressive disease is suspected (eg. MR.I of the brain should also be imaged, if brain metastases are suspected) per RECIST 1.1)(Section 17.3). If investigator makes a clinical diagnosis that

there has been p rogression, imaging examinations should be performed as promptly as possible, and effort should be made to obtain an image based assessment of PD. An1vIR.I of the brain is mandatory for all subjects included with baseline stab le brain metastases. Subjects without brain metastases do not need braill scan for fluuor assessment unless clinically indicated.

- Colle.ct blood samples for troponin (preferably high-sensi tivity troponin-T). The test used to test troponin should remain the same throughout the comse of a subject's time on study. An additional sampleshou]dbe submitted for central lab troponin-T le.sting.
- Obtain fresh mmor specimen from a subject at the end of treatmenif available. Tumor tissue will be sent to the ceutral laboratory for au exploratory biomarker an alysis . F mi her details will he provided in the laboratory manual. If the tumor is not taken, document the reason why the fresh tmnor sample is unavailable.

6.6. Fo llow- up

Fotfy days(+ 7 days) after last sn1dydmg administration or before starting new anticancer treatment. whichever comes first. tbe following procedures will be perfonued as specified in the Schedule of Events. If EOT is->40 (+ 7) daysafter last treatment, then tbe EOT assessments can also function as the F/U visit.

- Vita] signs (systolic and diastolic blood pressure, pu]serate. respiratory rate. body tempernture and Sp0 2).
- Physical examination.
- Weight will be recorded_
- ECOGPS.
- Hematology and blood chemistry assessmen ts will be perfonned.
- Senun or urine sample for pregnancy testing in women of childbearing potential.
- Collect blood samples for high sensitivity troponin (prefe:.rably troponin-T). 111e test used to test trnponin shouldremain the same throughout the course of a subject's time on srudy. An additionalsample should be submitted for central lab troponin-T testing.
- AEs and concomitant medications will be recorde,d
- For subjects with positive ADA at the F/U visit, additional serum ADA samples may be collected every *3* months (± 7 days) up to l year from the Jas t dose of study drug, or until the ADA becomes negative. or m1til the ADA titer becomes less than baseline (applicable wbe11 p1e-e x.isting ADA is observed), or until the subject starts another therapy for cancer, or withdraws consent from the study, whichever occurs first.

Subjects will also be assessed every 3 months (± 14 days), from the date of F/U ,risit, for smvival and subsequent anticancer therapy until death, withdrawal of consent, loss **to** F/U,

or study closure; whichever occurs first. This information may be collected in a visit or via phone contac,tor (as necessary for survival status, in thecase of withdrawal of consent or loss to F/U) from public records as allowed by law.

Further follow-up may be required for ongoing AEs (see Section 9.4).

A study visit schedule in tabular format is provided below in Section 18.

7. EFFICACY ASSESSME :rT s

7.1. Assessments for Efficacy Endpoints

7.1.1. Primary EfficacyEndpoint

Efficacy assessments will be based on tumor assessments to be peno1med at screening and every 6 weeks while the subject remains on study dn1g. The primary efficacy endpoint is ORR assessedby independentcentral imaging facility review based on RECIST version 1.1 in Coho11 A Refer to Section 17.3 for details regarding RECIST for radiological tumor assessments.

7.1.2. Seconda1y Efficacy End()oints

Secondary efficacy endpoints incJude DoR, OCR, PFS, OS, and ORR assessed by the investigator based on RECIST version 1. 1.

7.1.3. Exploratory Efficacy Endpoints

Exploratory efficacy endpoints include, time to respo nse, best percent change in the SLD of meas ura ble tumors, se n un HE R2EC D, and other biomarker analysis.

8. PHAR1VIACOKINETIC/PHAR.i'1L.\.CODYNAI\ilIC ASSESSMENTS

8.1. Pharmaco kinetic (PK) Assessments

Toe serum PK parameters listed in Table 8.1of DS-8201a, totaJ anti-HER2 antibody and I\1.AAA-118 la for each subject will be estimated using standard noncompartmental methods. The details of **PK** analysis will be specified in the Statistical Analysis Plan.

Table **8.1:** Phar macokinetic Parameters

	PK paramf'trrs
DS-8201a, total anti-HER2 antibody and I\iiAAA-11&Ia	Cmax, Tmax, AUClast and AUC 2K\ if appropTiate. AUCin(ti12, CL, and Vss

AUC210 = area under tl1e plasma concentrntmn-tlffie cun re up to Day 21, AUClast = area under the plasma concenu·ation-time curve up to the last quantifiable time. AUCinf = area under the plasma.concentrntion-time cm, •e up to infinity, CL: total body clearance, Cmax = maxinuun plasma concentrntion. t1n = tenninal elimination half-life. Tmax = time to reach mmtinmm plas ma concentration. Vss: volume of distribution ;it steady state.

Blood samples for DS-820 Ia PK analyses 1.vill be obtained at the time points specified in the Schedule of Events and in Table 8.2.

At each time point. blood will be collected for DS-8201a analysis. Tl1e actual time of study drng administration and the exact time of blood sampling for DS-8201a **PK** analysis must be recorded 011 the eCRF.

Instmciions for the handling of blood samples and shipping of semm samples for DS-820 Ia PK analyses are included in a separate document(ie, laboratory manual). Die DS-8201a PK samples: will be shipped to a ceutral laboratory for fon¥ardiug to a Sponsor designated bioanaly1ic al laboratory.

Table 8.2: Blood Sampling for Phc1rm acoki n e tic Analysis

Cycle	Day	Samplh1g Ti me Point (Acceptable Ran:ge)
Cycle l	Day 1	BI (- 8 to 0 hours) EOI: Wilhill 15 rninules after EOI 4 hours after r1le start of dmg adm iui s n·ation (± 15 minutes) 7 hours after the start of dlug adm inistration (± 2 hours)
	Day 8	7 days after the sta11 of dm g adminis1ration (± I day)
	Day15	14 days aftes the start of dmg admini stration (± 1 day)
	(Day 22)	If the sc:bedule on Day l of the next cycle is delayed for 3 days or more, including if rhe subject c.am1ot continue onto the next cycle. collect blood sam11)e 21 days after the start of drug administration (± 2 days). Iftbe next schedule is not delayed. sam:pliug at this point is not nec-essaiy
C'yde 2	Day I	**BI** (- 8 to 0 hours) EOI: Within 15 minutes after EOI
Cycle 3	Day I	BI (- 8 too hours) EOI: **Within** 15 minutes after EOI 4 hours after the start of dl1.1g adminisn·ation (± 15 minutes.) 7 hours after rbe start of dmg administration (± 2 hours)
Cycle 4	Day I	BI (- 8 too hours) EOI: **Within** 15 minutes after EOI
Cycle 6	Dayl	BI(- 8 to0 hours) EOI: Within 15 minures after EOI

Bl= before infusion. EOI = end of infitsiort

hi case of chloroquineor hydroxychloroquine administration for SARS-CoV-2 infection, additional PK sennn samples should be collected at the time points specified in Table 8.3. Tlie chloroquine or hydroxychloroquine administration time and the exact time ofbfood .samp ling for DS-820la PK analysis must be recorded in the CRF.

Table **8.3:** Schedule of PK Saml>le C o ll e ct ion fo r S u b je ct s Ad m ini st er ed C h loroq uine 01· Hyd t· xychJoroq uine

Day of CQ or HCQ Administration	Sa mpling Ti me Point (Accept able Ranges)
Day 1	Prior to *CQ/HCQ* dose
Day3 or Day 4	Prior to CQ/HCQdose (within4 hr-s)
End of *CQ* or HCQ treatment	Prior to CQ/HCQ dose (within 4 hrs)
P1ior to resumption of DS-820la (after CQ/HCQ wash-out period).a	Before infusion of study treament (within 8 hrs)

CQ = cltlornquiue, HCQ = hy(boxychloroquil e.
a washout period of no less dum J4 days is required before resumption of DS-820Ia~

8.2. Biomarker Assessments

In this study, biomarker analyses will be used to investigate the effect of the DS-820la at the molecular and ceJlular level as we11 as to deten u iue bow changes in the markers may relate to exposure and clinical outcomes. Tue sample collection infoimationas required sllould be recorded on the eCRF page(s) and central laboratory requisiiton fotm(s). Deta iled instructions for the collection, handling, and shipping of biomarker samples are out lined in the laboratory manual. Biomarker samples wiU be shipped to a central laboratory.

8.2.1. Pbarmacodyna.mk Assessments

821.1. Phat·macodynamic: Assessments ln Blood Samples

Pharmacodynamic biomarkers will be analyzed with the intent of mo nitoring the anti-tmuor impact of treatment with DS-820 l a. The pharmacodynamic biomarkers are HER2ECD and ctDNA. Blood samples will be collected for HER2ECD analysis at the time poinst specified in Tab]e 8.4, and cfDNA analys.is at the time points specified in Table 8.5.

Table 8.4: Exh·ace llular Domain of Human Epidermal Growth Factor Receptor 2 Sarnpli_ng Ti m e Point s

C ydr	Sam pling Ti me Point (Acct'ptable Range)
Screening	l. atest data within 14 days before Day 1 on Cycle I
Eveiy 2 cycles from Cycle 3 (eg, Cycle,3 5. 7, 9. IL .)	Within 3 days before adwinisrration
EOT	The date when the investigator decides on discontinuationof the sntdy·11eatment(+7 days).

EOT = end of lrei.lt meut.

Table 8.5: Cell Free Deoxyribonucleic Acid Sampling Time Points

Cyde	Sampling Time Poi.nt (Acceptable Range)
Cycle I Day I	Within 3 days before adminisrration
Cycle 4- Day 1	Within 3 days l>efore administration
EOT	The date when the invesrig-aror decides on discontinuat-ion of the study tJ·eaCment (+i days).

c:IDNA = ceU free deoxynbonucle1c acid. :EOT =end of treatment.

8212. Pharma codynamic Assessments in Tumor Specimens

Collection oftumor specimens is critical to assess the pha1macodynamic effect of DS - 820 Ia. Tim ing of sample collection is screening, at Day 43 and EOT. Tumor specimens will be used to assess the HERZ stanLs using IHC and/or ISH, and mRNA expression profile using NGS technology and or other methods.

8213. Additional Explo1·atory Biomu kel' Assessments

Dming the study. in addition to the biomarkers specified above. exploratory biomarker researc h may be conducted on any samples. These studies would extend the search for other :potential biomarkers relevant to the effects of DS-8201a. and/or the resistance to tb.e treatment. This mayinclude the development of ways to detect m011itor or treat cancer. These additional investigations wouM be depeudentupon clinical outcome, reagent and sam ple availa bili ty. If the patient agrees, the remaining samples (tumor tissues, blood and plasma) may be stored for up to 15 years.

8214. Dlsclosm·e of the Results of Additional Biomarket· Assessments

Because the nanll"e and val u e of future additional biomarker assessments is unknown at this time, any resultsobtained from research involving samples will not be disclosed to the subject or inve-stiga tors now or in the future.

8.3. SARS-CoV-2 Serum samples collection

Portion of HER2ECD blood sample from each subject who provides consent will be used for fo ture cen tra l lab ana lys is for SAR.S-CoV-2 testing. Samples **will** be sen t to the cen tral la boratory and store-d Ul!lti l tile te-sts will become available.

8.4. Pharmacogenom.ic Anal ysis

8.4.1. Genomic or Genetic Analysis

A single blood sampk for pha1macogenomicsanalysis will be collectedfrom each subject, who consented to this test on Day 1 of Cycle I_ P a rt icipa tion i n t hi s: part of the study is: optional for all subjects_

The fo ll o wingprocedures will be used for the long-tem1presetv ation (banking) of DNA spec.im ens extracted from subjects' blood samples. Pham1acogenomic samples may be analyzed for geues involved in abso1ption, distribution, metabolism, elilllination, safety, and efficacy of DS-820la. Additionally, samples may be ruialyzed for genes involved in DS-820la related signaling pathways. or to examine diseases or physiologic processes related to DS-820 1a. DN A samples will not be immorta lized or sold to anyone. This information may be us.efnl in increasing the knowledge of differences among individuals in the way they re.spond to the study dmg.

Specimen shipping and handling details will be included in tl1e laboratorymauual.

8.4.1.1. Dlsd osure of the Results of Genomic or G(!netlc Anal ysis

Beca use the nature and value of futu re phru m acogenomic research cannot be kno .rn at this time , a ny results obtained from research involviug pha1macogenomic samples will not be disclosed to the subject or investigators now or in the foture.

8.4.1. 2. Stora.g i' and Disposal of Specimen.s for Ge no mic or· Ge ne ti c Banking and Analysis

Samples •..vill be retained until exhausted or until the Sponsor requests disposition.

If tl1e subject witJ1drnws co nsent, the banked blood samples will be promptly managed regarding proper disposition. However. the data will not be discarded if genetic analysis has been completed before the subject withdraws consent.

8.5. Anonymlzation of Samples

l11e samples should be submitted to the courier without any personal information such as name that can be used to identify individuals. The samples should be identified by a llllque "site subject identifier." The coJTespondence list which can link the site subject iden tifie r and the persona] information should be kept su·ictlyat the study center and the linkage between the site subject identifier and personal info1mation should not be infonned the courier or the central laboratory. The sample.sand any other components from the cells collected for the additional biomarker assessment and phannacogenomic analysis will be stored in the central laboratory up to 15 years.

If the subject withdraws consent samples should be disposed of by the following procedure depending on the location of the nunor samples. Obtained data will not be discar ded if the assessm en ts have already beeu performed before consent was withdrawn. If samples are temporarily stored at tb.e study center, the investigator will identify tl1e samples oftbe relevant subject and dispose of them. If samples are stored at the central laboratory, the investigator will notify lhe sponsor about the identification number of the subject who withdrew consent The sponsor will inst.m et the central laboratory to dispose of the relevant samples. Eveunially, after the end oft.he sample storage period, the central laboratory will dispose of all samples as iustmcted by the sponsor.

8.6. Sa mple Storage .an d Disposal

TI1e samples and any other components from the cells collected for tlie additio11al biomarker assessment and phanuacogenomic analysis will be stored up to 15 years•

If the subject withdraws consent. samples should be disposed of by the following procedure depending on the location of the tum or sam ples. Obtained data will not be discarded if the assessments have aJrea.dy been petfonued before consent was withdrawn.

If samples are temporarily stored at tbe sn1dysite

- The investigator will identify the samples of the relevant subject and dispose of them.

If samples are stored at the central laboratory

- The investigator will notify the sponsor about the identification muuber of the subject who withdrew couseut. The sponsor will instrnct the central Iaborntoiy to dispose of therelevant samples.

Eventually, after the end of the sample storage period, the central laborntOiy will dispose of all samples as instrncted by the sponsor.

8.7. Immunogenicif:y (Anti-drug Antibody)

Blood samples for ADA analyses wilJ be collected at the time points specified in Section 6. A blood sample will be drawn at each time pomt. Senm1coucentrntio ns of DS-820la

and/or totaJ anti-HER2 antibody may be measured using the same ADA samples for purpose of ADA assessment.

Instrnctionsfor the handlingand shipping of ADA semmsamples are includedin a separate document (ie, laboratory manual). The ADA samples will be shipped to a central laboratory for fonvarcling to a SponsoJ designated bioanaJytical laboratory.

The inmmnogenicity testing "' Ll be pelfonued using validated ADA assay following tieredassay steps including screening, confumatory as well as titer determination. Samples confirmed positive will be banked until availability of the neutralizing anti-drng antibody assay.

9. SAFETY EVALUATION *Al* REPORTING

9.1. Ass essment of Safety Endpoint (s)

Safe ty p aram eters ·will in clude SAEs, TEAEs, ECHO/!vfUGA findings ophthalmologic findings, physical examination findings (including ECOG PS), vital sign measurements, standard clinical laborato1y parameters (blood chemistry and hematolog), ADA and ECG parameters. Adverse events will be categorized using the Ivledical Dictionary for Regu la tory Activities (MedDRA). Adverse events and abnormal laborato1y test results, if appl ica ble, wiU be graded using National Cancer Institute (NCD-CTCAE version 5.0.

9.2. Adverse Event Collection and Reporting

All clinical AEs (see Section 9.4.1 for definitions) occuning after the subject signs the Informed Consent Fonn for study participation and up to 40 (+ 7) days after the last dose (ie, the F/U period), ·wihether observed by the Investigator or repo1ted by the su bject , ,vill be recorded on the Adverse Event CRF page. For subje.cts who sign only the hlfonned Consent Fonn for tissue screening, repo11 only serious adverse events (SAEs) directly related to tissue screening prooedure (ie, tumor biopsy). Unless documentation of otl1er AEs is required by loca l law, only SAEs directly related to tumor biopsywill be recorded during tissue screening. :Medical condit ions (includ ing laboratory values/vital signs that are out of range) that were diagnosed or known to exist p1or to Infonned Consent will be recorded as part of medical history.

All AEs, SAEs. and events of special interest are to be reportedaccording to the procedures in Section 9.5 ..

.,\JI clin ical laboratory results, vital signs, and ECG results or findings should be appraised by the Inve sti gator to d etenu ine their clinical significance. Isolated abnormal laboratory results , vital sign findings , or ECG findings (ie, not pa1i of a reported diagnosis) should be reported as AEs if they are symptoma(i,dead to study drug discon inuation, dose reduction, require con ective treatment, or constitute an AE in the Investigator's cli.tli ca l judg m e nt.

At each visit, the Investigator will detenuine whether any AEs have occuned by evaluating the subject. Adverse events may be directly obse1ved, reported spontaueously by the subject or by questioning the subject at each sh1dyvisit. Subjects should be questioned in a general way, without asking about the occurrence of any specific symptoms. The Investigator must assess all AEs to detennine seriousness, seve1ity. and causality, in accordance with the definitions in Section 9.4. The h1vestigator's assessment must be clearly documented iu tile s ite's source documentation with the Investigator' s signa tur e.

Always repo11 the diagnosis as the AE or S AE term. When a diagnosis is unavailable. rep011 the prima1y sign or symptom as the A.E or SAE term with additional details included in the nanarive until the diagnosis becomes available. If the signs and sy1n.ptoms are distinct and do not suggest a common diagnosis, report them as individual entries of AEor SAE.

For events that are serious due to hospitalizatiou, the reasou for hosp italization must be reported as the serious adverse event (diagno sis or symptom requiring hospita)izatio n). A procedure is not fill AEoI SAE, but the reason for the procedure may be an AE or SAE Pre-planned (p1ior to signing the Infonned Consent Fonn) procedures or treatments requiriug hospitalizatio n for pre-exi sting co nditions that do uot worsen in severity should not be reportedas SAE s (see Sec tion 9A.2 for Definitions).

For deaths, the underlying or immediate cause of death sho uld always be reported as au SAE . Disease progression is a study endpoint and consequently, should not be reported as an AE/SAE. However, when a subject dies from PD with no other inuuediate causes, "diseaseprogression" should be reported as an SAE.

Any serious, untow ard event tliat may occur sub sequen t to the reporti ng pe1iod tliat the Investigator assesses as related to study drng should also be reported and managed as an SAE.

93. Adverse Events of Special Interest

Additional relevant information regarding the AESI's except iufusion-relate.d reactions specified below for the DS-820la clinical program will be collected tbrough the targeted questLonnaires , in-built within the eCRF in the study clinical database.

For broad smveiJlance of LVEF decrease. relevant AEs under the MedDRA SMQs of Cardiac Failure and 1vliocardial Infraction (Ml) are included for enhanced data collection additional data for these A.Es are collectedvia TQs of heart failme and ML

For broad surveillance of ILD, s.elected 42 PrefetTed Terms (PT) [all from the fLD Standard MedDRA Query (SMQ)] plus 2 PTs of acute respiratory failure and respiratory failure are included for euhauced data co11ections.

9.3.1. InterstlttaJ Lung Disease/PneumonUls

Clini cal S umm ary;

ILD /pn eumoniti s is considered au impoliant identified risk based 011 a comprehens ive ctUnulative review oftJ1e availab le safety data from the DS8201-A-Jl01 clinical srndy as well as the results of potential ILD/pneumontiis c ases reviewedby the independent ILD Adju dic a tion Committee (AC). available data from recent epidemiology/literature, biological plausibility, and safety information from drngs of similar class. Refer to the cunent IB for a sunuuary of preliminary clinical study data.

ManagementGuidance:

JLD/pneumonitsi should be mled out. if a subjectdevelops rndiograpbic changes potentially consistent with ILD/pnemmo niti s or de ve lo p s an ac ute o n se t of new or worsening pulmonary or other related signs/symptoms such as dyspuea, cough or fever. If the AE is confutned to have an etio]ogy other than ILD/pneumouitis, follow the manag em ent guidanc e outlined in Sec tion 5.4.

If the AE is suspected to be ILD/pneumonitis, treatment with shtdydrng should be intem.1pted pend ing further evaluations. Evaluations s hould include high resolution CT, pulmonologist consultation (infec tious disease consultation asclinic-all y indicated), blood culture and CBC (other blood tests could be considered as needed), bronchoscopy and

bronchoalveolar lavage if clinically indicated and feasible should be considered, pulmonary function tests and pulse oximetry (SpO 2), ruterial blood gases if clinically indicated, and one blood sample collection for PK analysis as soon as ILD/pneumonitis is suspected, if feasible. Other tests could be considered, as needed..

If the AE is confirmed to be lLD/pneumonitis, follow the management guidance in Section 5.4.

All events of ILD/pneumonitis regardless of severity or seriousness will be followed until resolution including after drug discontinuation.

9.3.1.1. Interstitial Lung Disease Adjudication Committee

An independent ILD Adjudication Committee for the DS-8201a program is responsible for reviewing all cases. of potential ILD/pneumonitis. To ensure adequate and relevant independent evaluation. systematic additional data collection will be conducted for all cases that will be brought for adjudication. These additional data collection will cover a more in-depth relevant medical history (eg smoking, radiation, COPD and other chronic lung conditions,)diagnostic evaluation , treatment and outcome of the event 111is data collection ·will be triggered for adverse evenst reported using selected 42 PT [all from the ILD Standard MedDRA Query (SMQ)] plus 2 PTs of acute respiratory failure and respiratory failure.

9.3.2. LVEF Decrease

Clinical Summary:

LVEF decrease in association with DS-8201a is considered to be an importanr potential risk based ou the available pre-clinical data, literature and available safety infonuation for drngs of similar class _ Refer to the current IB for a Slllmnary of preliminary clinical trial data.

Management Guidance:

LVEF will be measured by either ECHO or .MUGA scan . All ECHOs!MUGA,s·willl be evaluated by the investigator or delegated physician for monitoring cardiac function. Troponin will be measured at screening and after each infusion and EOTas needed based on subject reported cardiac signs or symptoms suggesting congestive heart failure. myocardial infarction. or other causes of cardiac myocyte necrosis. If ECG is abnormal. follow institutional guidelines.

Triplicate ECGs will be petfonued and standard ECG parameters ,:i.•ill be measured, including RR, PR, QT intervals. and QRS duration. All ECGs musr be evaluated by investigator or delegated physician for the presence of abnormalities. Whether or not measurement is perfo1med. date pelfonned. results. a.ad fmdings for each parameter will be recorded in the eCRF.

9.4. Adverse Event

9.4.1. Definition of Adverse Event

An adverse event is auy tmtoward medical occurreuce in a subject administered a phannaceutical product aud that does not necessarily have to have a causal relationship

with this treatment. A:n AE can therefore be any uufavorable and unintended sign (inc1uding an abnormal laboratory finding for exa1nple), symptomor djsease temporally associa ted with the use of a medicinal product, whether considered related to the medicinal product (International Council for Ha1morusation [ICH] E2A Guideline. Clinical Safety Data lvlaaagement: Definitfons and Standards for Expedited Repotting. Oct 1994).

It is the responsibilityof Investigatosr, based on their knowledge and expetience, to detemrine those c.ircumstances or abnormal clinical laboratory fmdings which should be considered adverse events.

9.4.2. Se1·lo us Adverse E,•ent

A se1ious adverse event is any untoward medical occunence that at any dose:

- Results in death,
- Is life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization,
- Results in persistent or significant disabili ty/incapacity.
- Is a congenital anomaly/birth defect. or
- Is an impmtant medical event

Note: TI1e tenu "life-threateuini' iu the definition of " serious" refers to an event in which the subject was at 1isk of death at the time of the event it does not refer to an event which liypothetically might have caused death if it were mo!re severe (ICH E2A Guideline. Clinical Safety Data Management: Definitions and Standards for Expedited Repottin, g Oct 1994).

Medical and scientific judgment. should be exercised in deciding whether expedited repo 1t in g is appropriate in other situatiollS, such as imponant me.die.al events that may not be inuu ediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. Examples include allergic bronchospasm, convulsions , and blood dyscrasias or development of drug dependency or dmg abuse.

Note:

- Procedures are not AEs or SAEs, but the reason for the prncedtue may be an AE or SAE.
- Pre-planned (prior to signing the fofonnerl Consent Form) procedmes or treatments requiring hospitaJizations for pre-existing conditions that do not worsen in seve1ity are not SAEs.

9.4.3. Seve rity Assess ment

All AEs wiU be graded (1 to 5: see befow) according to the latest NCI-CTCAE version 5.0:

- Grade 1 Mild AE

- Grade 2 Moderate AE
- Grade 3 Severe AE
- Grade 4 Life-threatening consequences; urgent interve ntio n indicated
- Grade 5 Death related to AE

Severitv versus Seriousness: Severity is used to describe the intensity of a specific event while the event itself, however, may be of relatively nni nor medical significan ce (such as severe 11eadache). Seriousness of an event *is* based upo n a tmiv ersal and global Regulatorydefinition for repotting SAEs to regulatory agencies. For example, Grade 4 (life threatening consequences; mgent iute1ventionindicated) is assessed based on unique clinical descriptions of severity for each AE, and tJ1ese criteria may be different from those used for the assessment of AE seriousness. An AE assessed as Grade 4 may or may not be assessed as serious based on the seriousness c1i teria. Overall, the severity of an event may be graded by the investigator as Grade 1 or 2. but if the subject presents to the emergency facility for evaluation and is hospitalized overnight foe obsetv ation that immediately makes the eventserious based upon hospitalization withoutregard t.o the investigator assess sm ent of severity.

9.4.4. Causality Assessment

TI1e Investigatorshould assess causal relationship between an adverse event and the study drng on the basis of his/her clinical judgment and the following definitions_ Tl e causality assessment must be made ba-sed on the available infm.mat ion and can be updated as new in.fonm1tiou becomes available.

- Related:
  - The AE follows a reasonable tem poral sequence from studydrug adrnit11stration, and cannot bereasonably explained by the subject>s cli nical s tate or other factors (eg. dise.ase under study, concunent diseases, and concomitant medications).

  or

  - The AE follows a reasonabeltemporal sequence from study dmg administ ration, and is a known reaction to the dmg m1der study or its chemical group, or is predicted by known pharmacology.
- Not Related:
  - The AE does not follow a reasonable sequence from st udy drug administrntion, or can be reasonably explaiim:l by the subject's clinical state or other factors (eg, disease under study, conc urrent diseases, and concomitant medications).

9.4.S. Action Taken Regarcllng S tu<l ' Dru g(s)

- Dose Not Changed: No change in study dmg dosage was made.
- Dmg Withdrawn: The study drng was pem1a11ent1y stopped.
- Dose Reduced: The dosage of study dmg was reduced.

- 0mg Inte1n1pted: Tue st:u<l y drug was tempormily stopped.

9.4.6. Other Action Taken for **Event**

- Nooe.
  - No treatment was required.
- Medication required.
  - Presc1iption and/or OTC medication was required to treat tbe adverse event.
- Hospitalizationor prolongation of hospitalization required.
  - Hospita1ization was required or prolonged due to the AE, whether or not medication was required.
- Other.

9.4.7. Aclverse E, ent Outcome

- RecoveredfR.esolve-d
  - The subject fully recovered from the adverse event ·with no residual effoct obse1ved.
- Recovering/Resolving
  - The adverse event improved but has not ful]y resolved.
- Not Recovered/Not Resolved
  - The adverse event itself is still present and observable.
- Recovere<ltRe.solved with Sequelae
  - l11e residual effects of the adverse event are still present and observable.
  - Include sequelae/residualeffects.
- Fatal
  - Fatal should be used when death is a direct outcome of the adverse event.
- Unknown

95. Serious Adverse Events a.nd A dverse Event of Special Interest Reporting-Proced ure For Investigators

All A.Es , SAEs , events of special interest, and medication errors including overdose will be reported ill the CRF.

Serious events that are also efficacy endpoints (eg, **PD) will** be exempted from SAE processing and expe.dited reporting. Disease progression should not be repo1ted as an AE/SAE. However, when a subject d ies from PD with no other immediate causes, "disease progression" should be reported as an SAE and captured on designated eCRF.

' These events are clinically anticipatedevents in the target treatment population, and wiH be periodically reviewe.d by tl1e Daiichi Sankyo safety teams to ensure prompt identification of any clinically coucenring safely issues.

TI1e follow ing types of events should be reported by the hlVestig ator in electronic data capture (EDC) within 24 hours of b oming aware:

- SAEs (see Section 9.4.2 for definition)
- Al l potential ILD case.s should be reported within 24 hours; including both serious and non-serious potential ILD cases (potential ILD is defined by the Event Adjudication Site Manual List of PTs).
- Hepatic events (both serious and non-serious) which meet the potential Hy's Law criteria defined as an elevated (ALT or Asn 3 *x* ULN and an elevated total bihmbin (TBL) >2 x ULN that may occur either at different time points or sim ultaneous ly dm-ing the study. A targeted questionnaire is built as an eCRF to collect relevant additional infonn ation for these potential cases.
- Overdose, defined as the accidental or inteutioual.ldministration of any dose of a product that is considered both exceoSs i ve and medically important. An "excessive and medically important" overdose includes any overdose in ·which either a se1ious adverse event, a. non-serious adverse event, or no adverse event occurs and is considered by the fuvestigator as clinically relevant, i.e. poses an acniaJ or potential risk to the subject.
  - Overdose is always serious. By definition an overdose is medically important, \Vhic h meets the seriousnes.s criterion of impo11ant medical event. An overdose can occm·with or without an AE. AEs can either be serious or uon-se1ious.Detai]s of the overdose including DS82Ola dosage. Clinical comse, associated AEs, and outcome nnust be cap tured in the Narrative form of the CRF within EDC.

All events (serious and non-serious) must be repo11ed with Investi gator's assessmen t of the event's setiousness, seveti ty, and causality to the study dmg. A detailed naITative s mllllarizing the com·se of the even t, incl uding its evalua tion, treatment, and outcome should beprovided. Specific or estimated dates of event onset, treatment, and resolution should be included when available. Medical bistoty, concomitant medications, and laboratory data that are relevant to the event should also be sunm1aiized it1 the nanative. For fat.,l events, the narrative sho uld state whether an autopsy was or will be performed, and include the results if available. Source doctunents (including medical reports) will be reta1i1edat t11e s n1dysite and shou]d not be submitted to the Sponsor for SAE reporting purposes.

Urgent safety que1ies rnust be followed up and addressed promptly. F/U infonnation and response to non-urgent safety queries should be combined for reporting to provide the most complete data possible within each F/U.

lu the event that eCRf is unavailable, repol't SAEs by faxing the paper Serious Adverse Event Repo1t (SAVER) Form to CRO using the provided fax trnnsmittal form and the appropriate fax number provided for your country. Once eCRF becomes available, please enter SAEs reported on the SAVER Fonn into eCRF as soon as possible. Pleaserefer to eCRF Completion Guilde for additional instrnctions.

See Section 15.12.4 for contact iufo1mation for SAE reporting . Please caJl the local SAE Hotline (see Study Ivtanual) or your sh1dy monitor for any questions on SAE repo1i11g.

96. Nofifying Regulatory Authorities, Investigators, and Institutional Revie,,, Board/Ethic.s Committee

Daiichi Sankyo andlor CRO will infonn Investigators, lRBs/ECs, and regulatory authorities of any Suspected Unexpected Serious Adverse Reactions (SUSARs) occuning in other study sites or other studies of the investigational drng, as appropriate per local repo11i11g requirements. Daiichi Sankyo and/or CRO will comply with any additional lo ca l safety reporting requirements.

In the US, upon receipt of the Sponsor's notification of SUSARs that occurred with the study drng, unless delegated to the Sp-0nsor, it is the Investigator's responsibility to inform the IR.B per Sponsor's instrnction.

In the European Economic Area states, it is the Sponsor's responsibility to repo11 SUSARs to all £Cs.

97. Exposure In Ute1·0 During Clinical Studies

DaiichiSankyo must be notified of any subject who becomes pregnant while receiving or within 7 months of discontinuing the s tudy drng.

Although pregnancy is not technic-ally an adverse event , all pregnancies must be followed to conclusion to detennine their outcome. This information is important for both dmg safety and public hea1t11 co ncerns. It is the responsibilityof the Investigator, or designee, to rep011 any pregnancy in a female subjectusing the Exposure h1 Utero (Elli) Reporting fonn. Please contact your sh1dy monitor to receive the EIU Repo1ting Form upon leaniiug of a pregnancy. The Investigator should make every effort to follow the subject until completion of the pregnancy and complete the ETIJ R:epo1ting Fonn with comp]ete pregnancy outcome information, including nom1al delivery and induced abo1tion. The adverse pregnancy outcome, either se1ious or non-serious, should be repo1te<l in accordance with study procedures. If the outcome of the pregnancy meets the criteria for immediate cJassification as a SAE (ie, post-partum complications, spontaneous or induced abo1tion, stillbiit h, neonatal death, or cougenital anomaly, including that il1an aborted fen1s,)the Investigator should follow the prooe<lmes for reporting SAEs outlined in Section 9.5.

98. Clinical Laboratory Evaluations

The following items will be measured. For clinical laboratoryparnmeters, the reference range of the institution that perfonns the measurements will be used.

Informatfoo will be entered in thecase report form on whether measured, date of measurement , and measurement results for the following items.

L Hematology tests

- Red blood cell count hemoglobin. hematocrit. platelet count. white b]ood cell count, differential white blood cell count (neutrophils, lymphocytes, monocyte s, eosinophils. basopbils).

2. Blood chemistry tests

- Total protein. albumin, alkaline phosphatase. ALT . AST. TBL , blood mea nitrogen/urea.calcium, chloride, senuu crea tinine, lactate dehydrogenase (LOH), potassimn, sodium, magnesium).
- A coagulation test will be perf01med (prothrombin. time a!lld act i va ted paitial thromboplastin time) and creatinine clearance (mL/min) wil.1 be ca l.cu late d using the Cockcrott-Gault equation (Section 17.l).

3. Utinalysis test
   - Protein, glucose, blood, micros.copy assessments (if indicated), and specific gravity

hi addition, the following parameters will be analyzedat the visits indie-ated in the Schedule of Events, Section 6.

- Pregnancy test (semm or urine) for all female subjects of childbearing potential must be performed during the Screening Period before each treatment cycle. EOT and F/U visit. A positive mine pregnancy test result must be confinned immeditaely using a senuu test. Test must be continued negative within 72 hours ptior to drug administratfon.
- Troponin (preferably troponin-T) test must be performed at the visits indicated in Section 18. Additional rrnponin testing shou ld be perfonned if subject repo11s cardiac symptoms. Same assay should be used for the sub-ject throughout their sn1dy participation.

All clinical laboratory values must be appraised iby the investigator as to clinical significance and used to t.ake appropriate c1ini.cal management measures. All abnornrn1 clinical laboratory values considered clinically significant by the investigator should be recorded on the AE page of the eCRF_ If the abnonnal laboratoty value constinnes an SAE, it will be repm1ed in the eCRF and othe·1relevant procedures must be followed (see Section 9.5). Abnmma1 laboratoty values (NCI-CTCAE grade 3 or 4) occuning during the clinical study will be followed until repeat test results return to n01mal (or baseline), stabilize, or are no longer clinically significant.

9.9. Vital Signs

Vital sign measurements ·will include systolic and diastolic blood pressure, pulse rnte, respiratory rate, and body temperature. Additionally, SpO2 **will** be measured at Screening, before administration on Day I of each cycle, EOT and F/U.

9.10. Electrocardiograms

Standa1-d sup i11e/se m i-recu mbe11t12-lead ECGs in triplicate (taken in close succession, 3 minutes apart) will be pe1formed as described in the Schedule of Events. Standard:ECG parameters "ill be measured, includingRR, PR, QT intervals and QRS duration. All ECGs must be evaluated by investigator or delegated physician for the presence of abnonnalities.

9.11. Physical Examinations

Physical examination findings including ECOG PS will be used to evaluate the following body systems/organs: general appearance dermatological; head and eyes; ears, nose, mouth, and throat; pulmonary: cardiovascular;abdominal; genitourinary (optional): lymphatic; musculoskeletal/extremities: and neurological. Weightand height will also be recorded in kilograms and centimeters, respectively.

9.12. Other Examinations

ECOGPS

Cardiac Assessments

- Either ECHO or MUGA, will be performed as described in the Schedule of Events (Section 6). LVEF will be measured

Ophthalmic Assessments

- Will includle visual acuity testing, sJit lamp examination, and fundoscopy_

Pulmonary Assessments

- Will includle CT or MRI of the chest, Sp0 2and will be performed as described in scheduleof events. For more details please refer to Section 6 of the protocol.
- An ILD Adjudication Committee (AC) will review all cases of (potential) ILD on an ongoingbasis. Description of the ILD AC is available in Section 9.3.1 _

10. OTHER ASSESSMENTS

Not applicable.

1.1. STATISTICAL :METHODS

11.1. General Statistical Considerations

The primary analysis \;vill be performed after all subjects have either discontinued the study or at least completed tumor assessment at 18 weeks (ie, at least 3 post-treatment tumor assessments) in Cohort A A data cut-off date for database lock will be identified for the primaryanalysis. After the pri1mary analysis, the data will be followed until c,ompletion.

Summary statistics will be presented by coh011. Co n tinuous variables will be summarized by the number ofobservation,smean, standard deviation, median, minimum, and maximum val ues (as well as geometric means and ge,ometric coefficient of va1iatjon for Cmax and AUC **PK** param eters) , unless otherwise specifie.d. Categorical variables will be S1munair-ized using frequency counts a11d percent age, s unless otherwise specified.

Assessment of ch:mge from baseline to post-treatment or the ratio of post-treatment to baseline will include only those subjects with both baseline and post-rteatment measuremen ts. The las t non-missing value of a variable taken before the first dose of the study dmg ,..vilJ be used as the baseJine value, unless otherwise specified. In genernl, miss ing or dropout data will not be imputed for the purpose of data analysis. unless otherwise specified.

Efficacy analyses will be perfonned on the full analysis set (FAS). Safety analyses will be peiformed using the Safety Analysis Set. Analysis of PK parameters will be based on the PK Analysis Set All other exploratory analyses will be petformed based on the FAS and the avaiIabiLity of assessments.

11.2. . Analysis Sets

11.2.1. Full Analysis Set/Safety Analysis Set

FAS/Safety Analysis Set will include all subjects who received at least I dose of the smdy dn1g.

11.2.2. Pbarmacokinet1c Analysis Set

The PK .Analysis Set will include all subjects who received at least 1 dose of the study drug and had measurable serum concentrations of DS-820la.

11.3. Study Population **Data**

Subject disposition will be summarized. The total number of subjec.ts for each defined analysis population will also be tabulated. The demographicand baseline characteristics will be summarized descriptively by cohort and overall for the FAS. Study drug exposure, treatment duration, and compliance with study tberapy as well as p1ior and concomitant med ications ,.vill be sumrnarized descriptively by cohort and overnU for the Safety Analysis Set.

11.4. Statistical Analyses

11.4.1. Efficacy Analyses

11.4.1.1. I'rimary Efficacy Analyses

The p1imary endpoint is ORR (the propo1tion of subjec ts who achieved a best overall response of complete response [CR] or PR) assessed by indep endent radiolog ic facility review in Cohd 1A. Confirmation of CR/PR is reqniied for this smdy.

Toe point estimate of ORR and its 2-sided exact 95% CI using Clopper-Pearson method will be provided by cohort. h1addition., ORR at the fLxed time points (eg, 6, 12, 18, and 24 weeks) along with their 2-sided exact 95% Cls using Clopper-Pearson method will be provided by cob011.

11.4.1.2. Seconclary Efficacy Analyses

TI1e secondary efficacy endpoints include ORR in Cohort B and Cobort C, DoR, DCR, PFS, OS, and ORR assessed by the iuvestigator.

Duration of response is defined as the time from the date of the first documentation of an objective response (CR or PR) to the date of the first documentation of PD. Duration of response will be measured for responding subjects (CR or PR) only. Detailed ceuso1ing m ies for duration of response will *be* specified in the statistical analysis plan (SAP).

PFS is defined as the time from the date of the first dose to the earlier of the dates of the first objective documentation of radiographic PD via independent radiologic facility review or death due to any cause. Detailed censoring mies for PFS wi11 be specified in the SAP.

OS is defined as the time from the date of first dose to the date of death from any cause. If the death of a subject is not reported before the data cut-off for OS analysis, OS will be censored at the last contact date at which a subject was known to be alive.

DoR, PFS, and OS will be su1mna1ized using Kaplan-Meier method with median event time and 2-sided 95% CI for the median using Brookrneyer and Crowley method by coho1t.

DCR will be analyzed in the same manner as ORR analysis. ORR assessed by the investigator will be analyzed in the samemam1er as the primary endpoint. Any additional analysis plans will be specified in the SAP.

11.4.1.3. E.xp lor ato•'Y Efficacy Analyses

ll1e exploratory efficacy analyses include subgroup analyses of the primary and secondary endpoints and analyses of exploratory efficacy endpoiuts.

11.4.1.3.l. Subgrnup Analyses

Subgroup analyses for ORR. PFS, and OS will be performed in Cohort A. Subgroup analyses will include:

- Lines of p1ior systemic therapy (2, 3, ::::,4)
- Age (<65, 65 yrs.)

- Sex (fernale, male)
- ECOG PS (0, 1)
- HER2 status (Cohort A: HER2 3+ or HER2 2+/ISH+)
- Primaty tumor site (Rectum, Colon)
- Histological subtype (Intestinal or Diffuse or Others)
- Number of metastatic sites (<2., 2)
- Pii.or treatment with irinotecan or other topoisomerase I inhibitors (Yes or No)
- Prior treatment with HER2 targeted regimen
- Prior treatment with any anti EGFR antibo dy or any VEGF antibody
- Piior tJeatment with regora.fen:ib or TAS-102
- Prior treatment witl1 anti-PD-l inhibitor
- Preseuce of non-liver metastasis at baseline (Yes or No)
- Renal impairment at base1ine (within uonnal range, and mildhnoderate impaim1ent)

In each subgroup defined above, the analysis will be canied out using the same type of methodology as described for d1e overall analysis of the co1Tespo11di11g endpoint.

11.4.1.3.2. Analys s of Explor ato1-y Effica cy E nd poin t!i

Time to response, and best percent change in tl1e S LD of measurable tumors will be evaluated and considered as exploratory efficacy endpoints.

Time to response wilJ ibe su llllnarized using Kaplan-Meiermethods with median event time and 2-sided 95% CI for the medi n using Brookmeyer and Crowley method by cohort.

Desc1iptive statistics for the best (minimum) percent change from baseline in the SLD will be provided. by coh011. Waterfull _plots of the best (minimum) percent change in the SLD for each subject will be presented by coho1i with vertical lines representing the sorted values of percent changes. Spider plots of the percent change in the SLD for e.ach subject will be also presented by coh01t.

11.4.2. Phal'maco.kinetic/Pharmacodynanlic/Biomarker Analys.es

11.4.2.1. Pharmacokinetic Analyses

Senuu concen trations for DS-820 Ia , total anti-HER2 antibody and MAAA-118 la will be listed, plotted, and smn mar-ized using descriptive statistics by cohort at each time point. PK parametesrwill be listed and summarized using d.escdptive statisticsby coho1.1

The population PK (pop-PK) ana lysis to evaluate the effect of intriusic and extrinsic factors of DS-8201a, and, if approp1iate, total anti-HER2 ant ibody and MAAA-118la will be characterized, including available PK data from the Phase 1 study. After establis hment

of the pop-PK model, a pop-PK/PD model will be developed to evaluate the relatiouship benveen exposure and efficacy and toxicity. The pop-PK and population pban nacoki :netics/phann acod ynamics (po p-PK/PD) modeling analyses may be repo11ed separatelyfrom the clinical study report.

11.4.2.2. Pharmacodynamic Analyses

Not applicable.

11.4.2.3. Biomai·ket·Analyses

Biomarkers Wm be listed and summarized using descriptive statisitcs.

11.4.2..4. Pharmacogenondc Analyses

Not applicable.

11.4.3. Safety Analyses

Safety analysis will be performed using the Safety Analysis Set. Safety analyses in general v1till be descrip tive and will be presented in tabu lar fonnat with the appropriate summary statistics.

11.4.3. 1. AdYer se E ve nt Anal yses

A TEAE is defined as au AE that emerges during the tJeatment period (from dateof first dose uutil the F/U visit after the last dose of the sh1dy dmg), having been absent at pre-treatment; or reemerges during treatment, having been present at baseline but stopped p1ior to treatment: or worsens in severity after starring treatment related to the pre-treatment state. when the AE is continuous. TEAEs will be coded using ivledDRA and assigned grades based on version 5.0 of the NCI-CTC AE. The number and percentage of subjects reponing TEAEs will be tabulated by system organ class (SOC), prefen-ed term (PT). relationshipto the study treatment. and the worst CTCAE grade. Sim ilarly, the number and percentage of subjects repo1ting treatmen t-emerge nt SAEs will be tabulated by coboct, as well as TEAEs leading to discontinuation of the sn1dy treatments.

A by-su bjed AE (including treatment-emergen) data listing including but not limited to the verbatim terms. SOC, PT, CTCAE grade. and relationship to study tre.atment wiU be provided. Deaths, other SA.Es, and other significant}\.Es, including those leading to discontinuationof the study ueatrnents, will be listed.

11.4.3.2. ClinicalLaboratory E,'alua.tion Analyses

Descriptive statistics will be provided by cohort for the clinical laboratory test results and changes from baseline by scheduled time of evaluation, as w·ell as for the change from baseline. In addition, the change from baseline will be summarized for the maximum post-treatmentvalue, and minimum post-treatmentvalue.

Abnormal clinical laboratory results wiH be graded according to NCl-CTCAE version 5.0, if applicable, and the gm.de will be presen1ed in a by-s ubjec t data listing. A shift table. presenting 2-way frequency tab ulation for baseline and the \vorst post-treatment value according to NCI-CTCAE grade, will be provided by coho11 for clinical laboratory tests.

All clinical laboratory test results and abnormal clinical laboratory test results deemed of cliniclasignificance orof Grade 3 or 4 will be listed.

11.4.3.3. Vital Sign Analyses

Desctiptive statistics wilJ be provided by cohort for die vital sign measurements and changes from baseline by sched uled time of evaluation. as well as for the change from baseline by scheduled time of evaluation, including d1e EOT visit and the maximum and minimum post-treatmat values. All vital sign data will also be listed.

11.4.3 .4. Elect1·ocardlogum Analyses

Descriptive st tistics will be provided by cohort for ECG parameters and changes from baseline by scheduled time of evaluation, including the maximum post-treatment values and the values at the EOT Visit In addition, the number and percentage of subjects with ECG interval values meeting tJ1ecriteria (eg, QTc 50 ms, >450 to 80 ms, >480 ms to 500 ms.and >500 ms) will be tabulated by cohort The QT intervals will be conecte-d for hea11 rate by Fridericia'5, formula ($QTcF = QT/[RR]^{113}$). ECG data will also be listed.

11.4.3.5. Anti-Drug Antibodies (ADA) Analyses

A shift table, presenting the 2-way frequency tabulation for baseline and all schedule times, including the EOT Visit, will be provided by c-0h01t for the incidence of ADA.

11.4.3.6. Other Safety Analyses

.-'\..ll other safety endpoints (eg, physical examination fin dings induding ECOG PS, ECHO/}.,fUGA, and ophthalmologic findings) will be listed.

1144 Other Analyses

Not Applicable.

11.5. Interim Analyses

No fonnal interim analyses are plarrned.

11.6. Sample Size Determination

A total of90 (Cohdl A: 50. Cohort B: 20. and Cohort C: 20) will be enrolled

Cohort A

The sample size of 48 subjects provides a 90% probability of achievmg a lower limit of 95% CI for the ORR tllat excee.ds 15% (threshold) under the expected ORR of 35%, and enables a statistical comparison with a histmical control on PFS (eg, provides a power of about 80% to detect the differenc-e in PFS nuder the assumption that median PFS will be prolonged from 2 months to 3 months compared to historical PFS in patients t1ea ted with regorafenib[21] or TAS-102[22]). Co nsidering drop out, 50 subjects will be enrolled.

Cohorts B and C

With this sample size, the probability that more than 4 responders out of 20 subjects (ORR > 20%) are obseitved wilJ be less than 5% under the threshold ORR of 10%, bu t mo re than 75% under the expected ORR of 30%.

The probability value for the sample size is derived based on binomial distribution using SAS® Version 9.3.

11.7. Statistical Analysis Process

The clinical study will be analyzed by OS or its agent/CRO followed by this protocol, and the SAP which will demonstrate all methodologies and displays/shells for statistical analyses.

The SAP will provide the statistical methods and definitions for the analysis of efficacy and safety data, and will describe the approaches to be taken to summarize other clinical study information such as subject disposition, demographic and baseline characteristics, study drug exposure, and prior and concomitant medications. The SAP will also include a description of how missing, unused, and spurious data will be addressed.

To preserve the integrity of the statistical analysis and clinical study conclusions, the SAP will be finalized prior to database lock.

All statistical analyses will be performed using SAS® Version 9.3 or higher (SAS Institute, Cary, NC 27513).

12. DATA INTEGRITY AND QUALITY ASSURA.t CE

The inve stigator/investigatio ual site \\l-ill permit smdy related monito1ing, audits, [RB/EC review and regulatory inspections by providing direct access to source data/documenst. Direct access includes permission to examin,e analyze, verify, and reproduce any records and repo1ts that are important to the evaluation of a di.nical study.

12.1. Monitoring and Inspections

The Sponsor, CRO monitor. and regulatory authority inspectors are responsible for contacting and visiting the Investigator for the purpose of inspecting the facilities and, upon request, inspecting thevarious records of the sh.1dy (eg , CRFs, source data, and other pertinent documets).

The verification of adherence to the protocol; completeness, accuracy, and consistency of the data; and adhere,nce to ICH Good Clinical Practice (GCP) aud local regulations on the conduct of clinical research ·will be accomplished through a combination of onsite visits by the monitor and review of study data remotel.yThe frequency of the monitming visit will vary based on the activity at each study site. The monitor is responsible for inspecting the CRFs and en.sudng completeness of the srudy essential documents. The monitor should have access to subject medical records a11d other study-relatedrecords needecl to ve1i.fy the entJ.ies on the CRFs. Detailed iufonnationis provided in the monitoring plau.

TI1e monitor will comnmntcate deviatjons from the protocol, SOPs, GCP and applicable regulations to the Investigator and will ensure that appropriate action (s) designed to prevent. rec1mence of the detected deviations is taken and documented.

The Investigator agrees to cooperate with the monitor to ensure that any problems detected in the comse of these monitoring visits are addressed to the satisfaction of the sponsor and docwnented.

In accordance with ICH GCP and the Sponsor's audit plans, this study site may be selected for audit by representatives firom tbe Sponsor. Audit of study site facilities (eg, pharmacy, drng storage areas, laboratories) and review of study related records will occur in orde r to eva luate the stu dy conduct and compliance ·with the protocol, ICH GCP, and applicable regulatory requirements, Tbe hwecStigator should respondto audit findings. In the event that a regulatory authority infonns the Investigator that it intends to conduct an inspect ion, the Sponso r shall be notified immediately.

12.2. Data Collection

The Investigator, sub-inves tigator , or study site staff will enter the data in the CRF in accordance with the CCGs that are provided by the sponsor to CRF completion should be kept cmTe11t to enable ithe mo nitor to review the subject's stanI.S throughout the course of the study, CRF will be completed,reviewed, aud e-signed by the Investigator according to the study data flow.

Any clinical data entered in the CRF will be subjec ted to these data management procedures and. will be included in the final study datasets according to CDISC standards.

OS or a designee will supply eCRFs. An eCRF must be completed for each subject who signs an ICF for study en tt)' and u ndergoe s any screening procedure. If a subject is not treated. the reason must be recorded on the eCRF. All data collected during the study will be recorded Ill this individual, subject-specific eCRF . In s trnc tion s will be provided for the completfon of the eCRF and any corrections made will be automatically documented via the EDC software's "audit trail."

Completiou of the eCRF should be kept cunent to enable the monitor to review the subject's status throughout the course of the study. All info1matio11 and other material to be used by subjects and investigative staff must use vocabulary and .language that a re clearly understood. 111e eCRF \Vill be completed, reviewed and si gned off or e-signed by the In, v es tiga tor. The fuvestigator will siga and date the indicated pla ces on the eCRF via the £DC system' s electronic signahue. TI1ese signatures will indicate that the Investigator inspected or reviewed the data on the eCRF, the data queries, and the site notifications, and agrees with the content. Tile infom1ation should be entered into the eCRF within 5 day s of the vis it and should be comple ted, reviewed , and signed off by the investigator within 2 weeks of the last subject visit_ Q uery resol uti on s hou ld be comp leted within 48 hours.

12 .3 . Data l\llanag ement

Each subject win be identified in the database hy a unique subject identifier as defined by the sponsor.

To ensme the quality of clinical data across all sub je c ts and stud y site s, a Clinical Data .tvlanagement review w ill be perfonned on subject data according to specifications given to Sponsor or Designee. Data "vvill be vetted both electronically and manually for CRFs and the data will be electronically vetted by programmed data rnles within the applicatio n_ Queiies generated by rules and raised by reviewers will be generated within the EDC applica tion. During this review, subject data will be checked for consisten cy, comp le teness and any apparent discrepancies.

Data received from externaJ sources such as ceutra.l la bs will be reconciled to the clinical database.

Serious Adverse Events in tbedinical database will be reconci1ed with tbe safety database.

All Adverse Events will be coded using MedDRA.

12.4. Study Documentation and Storage

111e Investigator will maintain a Sign a ture List of appropriately qua]ified persons to wbom he/she has delegated snidy duties. **All** persons authorized to make entries all(l/or conec.tions ou CRFs will be included on the Signa tu re List.

Investigators will maintain a confidential screening log of all potential study candidates that includes limited infonuation of the subjec,ts date and outcome of screening process.

Investigatosr will be expectedto maintain an Enrollment Log of all subjecst enrolled in the study indicating their assigned study number.

Investigators will maintain a confidential subject identification code list. This confidential list of names of all subjects allocated to study numbers on enrolling in the study allows the Investigator to reveal the identity of any subject when necessary.

Source documents are original documents, data, and records from which the subject•s CRF data are obtained. These include but are not limited to hospital records, clinical. and office charts, laboratory and phannacy reconts diaries, microfiches, X-rays, and cotTespondence.

Records of subjects, sourcedocumetus, monitoring visit logs, data correction fonns, CRFs, inventory of study drng, regulatory documents (eg, protocol and amendments, JRB/EC c01Tespondence and approvals, approved and signed informed consent forms, Investigator's Agreement, clinical supplies receipts, distribution and retum records), and other sponsor conespondence pertaining to rhe study must be kept in appropriate study files i\t the study site (Trial Master File). Source documents include all recordings and obse1va tions or notations of clinical activities and all rep01ts and recor ds necessary for the evaluation and reconstmction of tJ1e clinical study. TI1ese records win be ret1ined in a secme file for the period required by the institutio11 or study site policy. Prior to transfer or destruction of these records, the Sponsor umst be no tified in writing and be given the opportunity to further store such records_

12.5. Record Keeping

The luvestigator and study staff are responsible for maintaining a comprehensive aud centrahzed filing system (Trial Master File) of aJI sntdy-related (essential) documentation. suitablefor inspection at any time by representtaives from the Sponsor and/or applica.ble regu1atOiy authorities. Essential documents contained in the Trial :t\fa s te r File include:

- Subject files containing completed CRFs:, info n ned consent forms, and supporting copies of source docmnentatfon (if kept).
- Snidy files containing the protocol with all amendments , Inve s tigator ' s Brochure, copies of relevant essential documentsrequired ptior to commencing a clinical study, and all conespondence to- and from the IRB/EC1md the Sponsor.
- Records related to the study drng(s) including ack:ilO'wledgment ofreceipt at sn1dy ite, acco1rntability records and final reconciliation and applicable co rrespondence.

In addition, *all* original source documents suppo1ting ent1ies in the CRFs must be main tain ed and be readily available.

i\.ll essential docm:nentation will be retained by the institution for at least 5 years after comp le tion of the sn1dy or for a longer period, where so requi red by other applicable regulations or requirements. It is the responsibility of the Sponsor to infonu the in ves tigato r/institution as to when these documents no longer need to be retained. Subject' s medical files should be retained in accordance wit11 applicable legislation and in accordance with the maxirmun period oft ime permitted by the hospitaJ, institution or p1ivate practice.

No stud y docmuent should be destroyed without p1ior w1itten agreem en t between Sponsor and the Inve.stigator. Should the fuvestigator wish to assign the study records to another

party or move them to another location, he/she must notify Sponsor in writing of the new responsible person and/or the new location.

13. FINANCING AND INSURANCE

13.1. Finances

Prior to starting the study, the Principal Investigator and/or institution will sign a clinical study agreement with the sponsor or the CRO. This agreement will include the financial information agreed upon by the parties.

13.2. Reimbursement, Indemnity, and Insurance

The Sponsor provides insurance for study subjects to make available compensation in case of study-related injury.

Reimbursement, indemnity and insurance shall be addressed in a separnte agreement on terms agreed upon by the parties.

14. PUBLICATION POLICY

A study site may not publish results of a study Ulltil aJler a coordinated nmlticenter publicatio n has been submitted for publication or lmti.l I year after the study has ended. whichever occurs first. Therefore, the study site will have the opportunity to publish the resu]ts of thestudy, provided that Daiichi Sank.---yo has bad the oppmtunity to review and c-0mment on the study site's proposed publication p1ior to its being submitted for pu blica tio n with the prior advice of DS Legal Affairs (intellectual property council) and with proper regard to the protection of subjects' identities.

15. ETIDCS AND STUDY ADMINISTRATJVE INFORMATION

15.1. Compliance Statement, Ethics., and Regulatory Compliance

This study will be cond ucted in compliance with the protocol, the ethical principles that have their originin the Declaration of Helsinki, ICH consolidated Guideline E6 for GCP (CPMP/ICH/135/95), and applicable regulatory requirement(s) incJuding the following:

- US Food and Drug Administration GCP Regulations: Code of Fed eral Regulations (CFR) Title 21, pa11s 11, 50, 5<l, 56 , and 312 as appropriate and/or;
- Japanese Ministry of He.alili. Labor and Welfare Ordinance No. 28 of27 March. 1997 and/or;
- Direct ive 2001/20/E C of the Europe.au Parliament and of the Council on the approximation of the **laws**,. reg ulatio ns and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials 011 medicinal product for human use;
- Other applicable local regulations.

15.2. Subjed Confidentiality

The Investigators and the Spousor will preseive the c-0nfide11tiality o.f all subjects taking pa11 in the sn1dy, in accordance with GCP and local regulations_

For EU snidy sires, the Sponsor will observe the mies laid down in tile European Data Protection Directive 95/46/EC on the protection of individuals with regard to the processing of persoual data and the fre.e movement of sucli data.

The Investigator must el1Sure that the subject's anonymity is maintained. On the CRFs or other documents sub1nitted to the Sponsor or the CRO, subjects should be identified by a m1ique subject identifier as desiguatecl by the Sponsor. Documents tl1at arenot for submission to the Sponsor or the CRO (eg. signed ICF) should be kept in strict confidence by the Investigator_

In comp liance witl1 ICH GCP Gu idelin es, it is required that the Investigator and institution permit autbo1ized representatives of the companyof the regulatory agency(s). and the IRB/EC direct access to review the su bject' s original medical records for verification of sn1dy-relatedprocedures and data. The Investigator is obligated to inform the subject tliat his/her study-relatedrecords will be reviewed by the .abovenamed representatives without violating the confidentiality of the subject.

15.3. lnJ'or med Consent

Before a subject's participation in the smdy, it is the Investigator's responsibility to obtain ft-eely given- consent. ill writing, from the subject afteI adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the sh1dy and before auy protocol-specific procedures or any study dmgs are administered. Subjects should be given the opportunity to ask questions and rece ve satisfactory answers to their inquiries, and should liave adequate time to decide whether or not to participate in the study. The \1/1.itten !CF should be prepared u1 the local lau.guage(s) of the potential subject population.

In obtaining and documenting informed consent, the Investigator should comply with the applicable regulatory re<Juirements, and should adhere to GCP and to the ethical principles that have their origin in the Declaration of Helsinki. The consent form and any revision(s) should be approved by the EC or IRB prior to being provided to potential subjects.

TI1e su bject ' s written infonned consent should be documented in the subject' s medical records. Tue ICF should besigned and personally dated by the subject and by the person who conducted the intonned con.sentdiscussion (not necessa1ily the Investigator). l11e original signed ICF should be retained in accordance with instih1tional policy, and a copy of the signed consent fom1should be provided to the subject. TI1e date and time (if applicable) that infom1ed consent was given should be recorded on the CRF.

Suggested model text for tl1eICF for the study and any applicable subparts (geuomi<:, P K, e tc.) are provided in the Sponsor's ICF template for the Investigator to prepare the doc1m1ents to be used at his or her study site. Updates to applicable forms will be communicated via letter from the Sponsor.

For study site s in the US, an add ition a l consent is required for the Health Insurance Portability and Accotwtability Act (HIPA.A). Also, a separate special consent will be required for Pharmacogenomic testing for this protocol.

15.4. Informed Consent for Pharmacogenomic AnalysL

Before obtaining samples for pharmacogenomic allillysis , the investigator is responsible for obtaining freely given consen,t in writing, from tile subject, after giving an explanation of the phannacogenomic analysis in intelligible terms_ Before obtaining the infonned consent the investigator should provide the subjects with adequate time to have the oppo11unity to inquire about the detai ls of the study, and should answer all questions properly. This analysis is an optional anaJysis for whomagreed to join cJinical study , and another ,v1itten.infonned consent docmuent is prepa,red, separately from iufom1ed consent for clinical study.

15.5. . Reg ulat ory Compliance

l11e study protocol, suibject infonnation and consent form, the Investigator Brochme, any subject written i.nstmctions to be given to the subject. available safety inforrnation. subject recmitment procedures (eg, advertisements), .info rma tion about paym.ents and compensation available to the subjects, and documentation evidencing the Iuvestigator's qualifications should be submi tted to the EC or IRB for ethical review and approval according to local regulations, p1ior to the study stai1. The \VIitten approval should identif y all documents reviewed by name and version.

Changes iu the conduct of the study or planned analysis will be documented in a protocol amendmenr and/or the SAP.

The Investigator and/or Spon sor must submit and , where uecessa1,yobtain approval from the EC or IRB for all subsequent protocol amendments and changes to the ICF. The Iuvestigator should notify the EC or IRB of deviations from the protocol or SAEs occmTing at the study site and other AE repmts received from the Sponsor /CRO , in accordance with local procedures.

As required by local regulations, the Sponsor's local Regulatory Affairs group or representative to v\lhom this responsibility bas been delegated will ensure all legal aspects are covered, and approval from the appropriate regulatory bodies obtained, prior lo s tudy initiation, and that implementation of changes to the initial protocol and other relevant study documents happeu only after approval by the relevant regulatory bodies.

fu the event of any prohibition or rest:1iction imposed (eg. clinical hoJd) by au applicable Regulatory Autho1ity(ies) in any area of tlle world. 01· if the Investigator is aware of any new infonnation which might influence the evaluation of the benefits and risks of the investigational dmg, tbe Sponsor should be info1med immediately.

In addition, the Investigator wiH infonn the Sponsor immedia tely of any urgent safety measures taken by the Investigator to protect the study subjectsagainst any immediate hazard. and of any suspectecVactual se1ious GCP non-compliance that the Investigator becomes aware of

15.6. Protocol Deviations

The Investigator sliould conduct tile study in compliance \>Yitli the protocol agreed to by Sponsor and, if required, by the regulatory authority(ies), and which was given approval/favorable opinion by the IRBs/ECs.

A deviation to any protocol procedme or waiver to any stated c1itetia will uot be alJowed in this study except wl!ere necessary to eliminate immediate llazard(s) to the subject. Sponsor must benotified of all intendedor unintendeddeviations to the protocol (eg. inclusion/exclu:;ioncriter,ia dosing, missed study visits) on ru1 expedited basis_

l11e h1vestigator. or persou designated by the h1vestigator, should document and explain any deviation from the approved. protocol.

If a subject was ineligible or received U1e incorrect doseor study treatment, and had al least 1 administration of study dmg, data should be collected for safety pmposes.

If applicable, the Investigator should notify the IRB/EC of deviations from the protocol in accordanc.e with local procedures.

15.7. Supply of New Inforn1ation AJTec ting the Conduct of the Study

When new infonnatiou becomes availa ble that may adversely affect the safety of subjects or the conduct of t11e s1:ndy, the Sponsor will inform all Investigators involved in the clinical study, IRBs/EC s, and regulatory autbo1itie-S of such infomiation , and when needed. will amend the protocol and/or subject infomiation.

l11e Investigator should immediately i nform the subject whenever new information becomes available that may be relevant to the subject' s consent or may influencethe subject's willingness to continue pa1 lìpation in the smdy. Tue communicacion should be documented on medical records, for example, and it should be c-0nfnmed whether the subject is willing to remain in the study.

If the subject information is revised, it must be re-approved by the IR B/EC. The Investigator should obtain writteu infonned consent to continue participation with the revised written information even if subj ects were already infonne-d of the relevant

information. TI1e Inv estigato r or other responsible personnel who provided explanations and the subjectshould sign and date the revised ICF.

15.8. Protocol Amendments

Any amendments to the study protocol that seem to be appropriate as the study progresses will be communicated to the Investiga tor by Daiichi Sank-yoor the CRO. Also, the Sponsor will ensure tbe timely submission of amendments to regulatoryautl1orities.

A global protocol amendment will affect study conduct at all study site s in all regions of the world. Such amendments ·will be.inco rporated into a revised protocol document. Changes made by such amendments will be documented in a Summa ry of Changes document. 111ese protocol amendments vv·il1 undergo the same review and approval process as the original protocol.

A local protocol amendment will affect study conduct at a paJ.iicular s tudy site(s) and/or in a pruticular region/countty. Sponsor approval ofl ocal amendments **will** be clearly documented.

A protocol amendment may be implemented after it bas been approved by the IRB1EC and by regula toy1 autho1ities ·where appropriate, unless iillllledia te implementation of the change is necessary for subject safety_

15.9 . St u dy Termination

The Spomor has the right to terminate the study at any time and study termination may also be requested by (a) competent authority (ies).

15.10. Data and Safety Monitoring Board

Not applicable.

15.11. Steering Committee

A steering committee **will** be established for this sn1dy. Details on the membership. responsibilities. and working procedures of the committee will be described in its own charter.

15.12. Address List

A list of key studypersotmel (including personnel at the sponsor. CR O, laboratories, and other vendors) and their contact infomiation (add1ess, telephone, fa....., em ai l) will be kept on file and regularly updated as necessary.

15.12.1. Sponsor

Japan
Daiichi Sankyo Company. L imi ted
3-5-1, Nihonbash-houcho, Chuo-bi, Tokyo 103-8426, Japan

US
Daiichi Sank-yo, Inc.

211 Mt Ai1y Rd.
Basku\\z Ridge. NJ 07920, USA

15.12.2. Sponso, r s Responsible Medical Officer

pPI)

lv1edical Monitor
211 Mt Airy Rd.
Baskill'st Ridge. NJ 07920. USA
PPO ""

[redacted]

15.12.3. . Sponsor's Clinical Study Leader

PPD
PPD
[redacted]

15.12.4. Sponsor's Cli nical Opera tion s Delh·e11' Lead

PPO

[redacted]

15.12. . Spo·nsor 's S afe ty C ont act

f/Ja_n

3-5-1 Niboubashi-boucbo, Chuo-ku, Tokyo 103-8426. Japan
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Clinical Safety and Pharmacovigilanc,e
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Baskim2: Rid e NJ 07920, USA
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15.12.6. ARO

Not applicable.

15.12.7. CROs

Syneos: Health
3201 Beechleaf Corn--t Suite 600
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Covance Inc..
206 Car11egie Ceuter
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PPD

15.12.8. Vendor of Interactive \'Vcb Response System

Almac group.
25 Fretz Road Souderton, PA 18964
PPD

15.12.9. Central Laborntory

Covance Central Laboratory Services.
8211 SciCot' Drive
Indianapolis, IN 46214
PPD

Ventana Medical Systems, Iuc.
1910 Innovation Park Dr. Tucson, *AZ.* 85755 USA.
PPD

Guardant Health. Inc.
505 Penobscot Drive
Redwood City. CA 94063 U.S.A.
FPO

Daiichi Saul)'o RD Novai·e Co., Ltd.
1-16-13 Kitakasai. Edogawa. Tokyo 134-8630. JAPAN
PPD

15.12.10. Centr1d Im.aging

Bioclinica Inc.
211 Carnegie Center, Prin ce to,n NJ 08540
PPD

15.12.11. Bioanolytical Laboratory (Pbarmacokinetics and Anti-drug Antibodie)

PPO
2244 Dabney Road
Richmmnd, VA 23230. USA
PPD

15.12.12. ponsor>s Biostatisticinn

r

1-2-58 Hiromachi, Shinagawa-ln1, Tokyo 140-8710, Japan
PPD

15.12.13. Data Safety Monitoring :Board

ot applicable.

16. REFERENCES

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17. APPENDICES

17.1. Cockcroft-Gault Equation

The estimated creatinine clearance rate (CrCl; mL/min) will be calculated using the Cockcroft-Gault equation based on actual weight in kilograms (1 kilogram = 2.2 pounds):

Conventional- serum Creatinine in mg/dL:

Male:

$$\text{CrCl (mL/min)} = \frac{[140 - \text{age (in years)}] \times \text{weight (in kg)}}{\text{serum creatinine (in mg/dL)} \times 72}$$

Female:

$$\text{CrCl (mL/min)} = \frac{[140 - \text{age (in years)}] \times \text{weight (in kg)} \times 0.85}{\text{serum creatinine (in mg/dL)} \times 72}$$

International System of Units (SI) - **serum** creatinine in µmol/L:

Male:

$$\text{CrCl (mL/min)} = \frac{(140 - \text{age (in years)}) \times \text{weight (in kg)}}{\text{serum creatinine (in µmol/L)} \times 72 \times 0.0113}$$

Female:

$$\text{CrCl (mL/min)} = \frac{[140 - \text{age (in years)}] \times \text{weight (in kg)}}{\text{serum creatinine (in µmol/L)} \times 72 \times 0.0113} \times 0.85$$

Source: Cockcroft OW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976;16:31-41.

17.2. Eastern Cooperative Oncology Group Performance Status (ECOG PS)

Table 17.1: Eastern Coo1lerat1veOncology **Group Perfo·tmance Status** Scale

0	Nonnal activity. Fully active, able to cany 011 a11 pre-disease perfonnance without restriction.
1	Symptoms, but ambulato1y. Resllicted in physically su·enuous activity, but ambulatory and able to can)' out work of a Jight or sedentary nature (eg. ligbt housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waling hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair mnore than 50% of waking hours.
4	100% bedridden. completely disabled. Callllot c.arry on any self-care. Totally confmed ito bed or chair.
5	Dead.

Source: Oken MM Creech RH. Tonney DC, H01ton J, Davis TE , McFadden ET. el at Toxicity and Response Criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982:5:649-55.

17.3. Respon se Evalua tion Criteria in Solid Tumor s, Version 1.1

17.3.1. Measurability of Tumor at Baseline

173.1.1. Definitions

At baseline, nunor lesions/lymphnodes wdl be categotized measurable or non-measurable as follows:

17.3.1.1.1. Measurable

- Tumor lesions: Must be accurately measured in at least I dimension (longest diameter :in the plane of measurement is to be recorded) with a minimmn size of
  - IO mm by CT scan (CT scan slice thickness no greaJer than 5 mm)
  - IO nun caliper measurement by cli11ical exam (]esions which ca1111ot be accurately measured with calipers shou ld be recorded as non-measmable)
  - 20 mm by chest X-ray
- Measurable malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be 15 mm in sh01t a-xis when assessed by CT scan (CT scan sUce thickness recommended to be no greater tllan 5 mm). At baseline (ie, screening for this study) and in F/U (ie. all measurements past screening for this study}, only the sh011axis will be measured and followed. See also notes below on "Baselinedocument.ation of target and non-target lesions" for infounation on lymph node measurement.

17.3.1.l.2. Non-1\ileasun bJe

All other lesions, including small Jesions(longest diameter <l O mm or pathological lymph nodes \\lith 10 to <15 mm sh011axis), as vvell as truly non-measurablelesions. Lesions considered trnly non-measurable include: leplomeningeal disease, ascites, pleural or pericardia! effusion, inflammatory breast disease, ly111phan gitic inv olvemen t of skin or lung, and abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reprnducible imaging te.chniques.

17.3.1.l .3. Special ConsideraCio ns Rega r di n g Les i o n Measurability

Bone lesions. cystic lesions. and le.sions previously treated with loca! therapy require particular comment.

17.3.1.l .3.l. Bone Lesions

- Bone scan, positron emission tomography scan or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confim1 tlie presence or dlisappearance of bone lesions.
- Lytic bone lesions or mixed l}lic-bl astic lesions, with identiliable soft tissue components, that can be evaluated by cross-sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above.
- Bla stic bone lesions are non-measurable.

17.3.J.l. 3.2. Cystic Lesions

- Lesions that meet the etiteria for radiographically defined simple cysts shouJd not be considered as malignant lesions (neither measurable nor non-measmable) since they are, by definition , simple cysts.
- "Cystic lesions" thought to represent cystic metastases can be considered as measurable lesions, if they meet tl1e definition of measurability described above. However,if noncystic lesions are1Jrese nt in the same subject, these are prefe1Ted for selection as target lesions.

173.1.133. Lesions with Prior Local Treatment

- Tumor lesions situated in a pirevious l y ilrn dia ted a1ea, or in an area subjected to other loco-regional t11erapyare not considered measurable m1less there bas been demonstrated progreBsion in the lesion.

17.3.1.2. Speclflcatlons by .Methods of :Measurements

17.3.1.2.1. Measurement of Lesions

All measurements should be recorde.d in metric notation. using calipers if clinically assessed. All baseline evaluations should be perfonned as close as possible to the treatment sta11 and NEVER more than 28 days before enrollment(study treatment).

17.3.1.2.2. Method of Assessment

Toe saline method of assessment and the same technique should be used to characterize each identified and repo1ied lesion at baseline and dming F/U. Imaging based evaluation should always be performed rather than clinical examination unless the lesion(s) being foJlowed cannot be imaged but are assessable by clinical exam.

CT, ivlRI: CT is the best cunently available and reproduciblemethod to measure lesions selected for response assessment. Th.its g uideline has defined measurability of lesionson CT scan based on the assump tion that CT slic,e thickness is 5 mm or less. 'When CT scans have slice thickness greater than *5* mm, die minimum size for a measurable lesion should be twice the slice thickness. .MRI is also acceptable in certain situations (eg, for body scans).

17.3.2. Tumor Response Evaluation

17.3.2..1. Assess men t of Ovenll Tumor Burden and Measurable Disease

To assess objective resporu.e or futme progression, it is necessary to estimate ilie overall tumor lburd en at baseline and use this .as a comparator for subsequent measurements_

In this study, only subjects witJ1 measurable disease at baseline should be included.

17.3.2.2. Baseline Documentation ,of "Target" an(l "Non-tar get" Lesions

When more than 1 measurable lesion :is present at baseline, all lesionsup to a maximum of *5* lesions total (representative of all involved organs) should be identified a:s tar ge t le sions and will be recorded and measured at base.line (this means in instances where subjects have only 1 or 2 organ sites involved a maximum of 2 and 4 lesions respectively will be recorded).

Target lesions should be selectedon the basis of tl1eir size (lesions with the longest diameter), be representative of all involved organs , but in add itio n should be those tbat lend themselves to reproducible repeated me-asurements. It may be the case that on occasion, the largest lesion does not lend itself to reproducible measurement in \.\lticb cir cu ms tance the next largest lesion which can be me.asured reproducibly should be selected.

Lymph nodes merit special mention since they are no1111al anatomical stmcnu·es which may be visible by imaging even iJ not involved by tumor. As noted above. pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of 2:15 mm by CT scan. Only the short axis of these nodes will conttibute to the baseline su,m Tue sbort axis of the node is the diameter nonnaUy used by radiologists to judge if a node is involved by so lid tumor. Nodal size is nom1ally reported as 2 dimensions in tl.1e p lan e in which the image is obtained (for CT scan tl1is is almost always the axial plane; for:rvoo the plane of acquisition may be axial. sagittal, or coronal). The sma.Uer of these measure-s is the short axis. For exampl e, an abdominal node which is reported as being 20 mm x 30 mm llas a short axis of 20 mm and qualifies as a mali gnant, measurable node. In tl1is examp le, 20 mm should be recorde d as the node measurement. All other pathological nodes (those with short axis 10 mm but <15 nun) should be considered non-target lesions. Nodes that have a short axis <10 mm are cons ide red non-pathological and should not be recorded or followed.

A sum of the diameters (lougest for non-nodal les ions, short axis for uodal lesions) for all target lesions will be calculated and reported as the baselinesmn diameter s. If lymph nodes are to be included in the sum. then as noted above, only the short a.xis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of tl1e disease.

All other lesion s (or sites of disease) il1cluding pathological lym ph node s shouldbe identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be fo llowed as "pre.sent," "absent." or inrare cases "unequjvocaJ progres s.ion." In addition, it is possib]e to record multiple non-target lesions involving the same organ as a single item on tl1e case record form (eg« multiple enlarged pelvic lylllph nodes" or "multiple liveJ" me tastases ").

17.3.2.3. Response Criteria

This section provide.s the definitions of the crite1i a used to detennine objective tumor response for target lesions.

17.3.2.3.1. Evaluation of Target Lesions

CR: Disappearance of all tal'getlesions. Any pathological lymph nodes (whetJ1er tai·get or non-target) must have re-duction in short axis to <lO mn1.

PR: At least a 30% decrease in the sul!Il of diameters of target lesions. taking as refe1·ence the baseline sum diameters.

PD: At least a 20% increase in the sun.1of d iam ete rs of target lesions, taking as reference the smallest sum on study (this include s the baselinesum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least *5* mm. (Note: the appearance of 1 or more new lesions is also considered progression.)

SD: Neither sufficient shrinkageto qt1alify for PR nor sufficientincrease to qualify for PD. taking as reference the smallest sum diameters ·while on study.

17.3.2.3.2. Special Notes on the Assessment of Target Lesions

Lymph nodes: Lymph nodes identified as target lesions should always have the actual shon 1U<is measurement recorded (meastued in the same anatomical plane as the baseline examination). even if the nodes regress to below 10 mm on study. This me.ans that when lymph nodes are included as target lesions, the "sum" of lesions may not be zero even if CR criteria are met, since a nonuaJ lymph node is defined as having a shott axis of <10nun. For PR, SD, and PD, theacmaJ s hort axis measurement of the nodes is to be included in the sum of target lesions.

I a1·getJe. ions that become Ht o o **small to measu1•e":** While on study, all lesions (nodal and non-nodal) recorded at baseline sl10uld have their actual measurements recorded at each subsequent evaluation, even when very small (eg, 2 mm). However, sometimes lesions or lymph nodes which are recorded as target lesions at baseline become so faint on C'T scan that the radiologist may not feel comfortable assigning an exact measure and may reprnt tl1e111 as being "too small to measure." ·when this occ1us, it is important that a value be recorded on the eCRF. If it is the opinion of the radiologist that U1e lesion bas likely disappeared, the measurement should be recorded as 0 rwn. ff the les ion is believed to be

present and is faintly seen but too smalJ to measure, a default vaJue of 5 mm should be assigned. (Note: It is less likely that this rule will be used for lymph nodes since they usually have a definable size when no:m1al and are frequently sunounded by fat such as in the re tro per iton eurn; however, if a lym ph node is believed to be presen t and is faintly seen but too smaJI to measure, a default vaJue of 5 mm shou ld be assigned in this circumstance as well.) Tlris default value is derived from the 5 mm CT slice thickness (but should not be changed with varying CT slice thickness). The rueasurement of these lesions i.s potentially non-reproducible, therefore providing this default value wiH prevent false responses or progressions based upon measurement eITor. To reiterate, howeve,riJ tbe radiologis t is able to provide an actua1measure. that should be recordecL even ifi t is below 5 mm.

Lesions that split or coalesce on treatment: Wl1en non-nodal lesions " fragment," **the** longest diameters of the fragmented portions should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a planebeiween them may be maintained that wo uld aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have tmly coalesced such tl1at they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the " coalesced lesion."

17.3.2.3.3. Evaluation of **Non-target** Lesions

This section provides the definitions of the criteria used to detennine the tumor response for the group of non-target lesions. \While some non-target lesions may actually be measurable , they need not be measured and instead should be assessed only qualitatively at the tin1e points specified in the protocol.

CR: Disappearnnce of all non-target lesious and uonnalization of tumor marker level. *All* lymph nodes must be n on-p athol ogica 1 in size {<IO mm sho1t axis).

Non-CR/Non-PD: Persistence of 1 or more non-target lesion(s) and/or maintenanceof tumor marker level above the nonnal limits.

PD: Unequivocal progression (see comments below) of existing non-target lesions (Note: the appeanmce of 1 or more new lesions is also considered progression).

17.3.2.3.4. Specia1 Notes on Assessment of Prog1·esasion of Non-tal· ge t Dis ea s e

TI1e c oncept of progression of non-target disease requires additional explanation as follows:

Wben the subjectalso has measurable disease: In tbis setting, to achieve "unequivocal progression" on the basis of the non-target disease, there must be an overall level of substantialworsening in non-targetdisease such that , even in presence of SD or PR in target disease, the overall tumorbmden bas increased sufficiently to metit discontinuation of therapy. A modest " increase" in th.e size of 1 or more non- targe t lesions is usually not sufficient to qua lify for unequivoca 1 progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of SD or PR of target disease will therefore be extremely rare.

When the subjecthas only non-measurable disease: TI1e sa me gent!ral concepts apply here as noted above. however. in this instance there is no measurable disease assessment to

factor into the interpretation of an increase in non-mea surable disease burden. Because worsening in non-target disease cannot be easily quantified(by definition: if all lesions are trnly non-measurable) a useful tes t that can be. applied when assessing subjects for unequivocal progression is to consider if tbe. increase in overall disease burden based on the cha.nge in non-measurable disease is comparable in magnitude to the increase tliat wou ld be required to dedare PD for measurable disease (ie, an increase in tumor burden repres enting an additio nal 73% increase in ·'volume" [which is equivalentto a 20% increase diameter in a measurable lesion]). 1f ·unequivoal progression' is seen, the subject should be considered to have had overall PD at that point. '\\'bile it would be ideal to have objective c1ite1ia to apply to non-measurabledisease, the Vet)' nature of that disease make.s it im possible to do so therefo re the increase must be substantial.

17.3.2.3.5. Nev·. Lesions

l11e appearance of new malignant lesions denotes dis.ease progression ; therefore , some comments ou detection of new lesions are impo11ant. There are no specific c1iteria for the identific:ation of new radiographic lesions; however, the finding of a new lesion should be unequivocal: ie, not attributable to differences in scanning technique, change in imaging moda lity or findings thought to represent something other than tmnor (for example, some "new" bone lesions may be simply healing or flare of preexistinglesions). l11si is part icula rly impo11aut when the subject's baseline lesions show PR or CR. For exam ple, necrosis of a liver lesion may he repm1ed on a CT scan repo1t as a " new" cystic lesion, which it is not.

A]esion idet1tified on a FtU snidyin an anatomical]ocation that was not scanned at baseline is considered a new lesiou aud ·will indicate disease progression. An example of this is the subject who hasvisceral disease at baseline and while on study has a CT or :MRI bra in ordered which reveals metastases. The subject' s brain metastases are considered to be evid nce of PD even if he/she di<J not have brain imaging at baseline.

If a new lesion is equivocal, for example because of its small size, continued therapy and F/V ev3luation will clarify if it represeuts trnly new disease. If repeat scans coufum there is definitely a new lesion, then progression should be declared using the date of the initial scan.

17.3.2.4. Evaluation of Best Overa ll Res1>0nse

The best overall response is the best response recorded from the start of the study treatment until the EQT. Confirmatory measurement for CR, PR, or SD is req uired in the study.

Tue subject's best overall response assignmentwill clepend on the findings of both target and non-target disease and will also take into consideration the appearance of new lesions.

17.3.2.4.1. Time Point Response

It is assumed that at each protocol-specified time point, a response assessment occurs. Table 17.2 provides a summary of the overall response status calculation at each time point for subjecst who have measurable disease at baseline.

\llheu subjects have nou-measurab]e(tl1erefore non-target)disease only, see Table 17.2.

Table 17.2: Overall Response: Subjects with Target (± Non-ta1·get) Disease

Ta1·getlesions	Non-targe t Ies io o.s	Ne" ' les ions	O ve rall rt'spo m,e
CR	CR	No	CR
CR	Nou-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all Evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR= complete response. PR= paitial response. SD= stable disease, PD= progressive disease. NE = not evaluable.

17.3.2.4.2. Missing Assessments and Inevaluable Designation

\Vhen :no imaginglmeasurement is perfmmed at all at a particular time point, tl1e subject is not evaluable (NE) at that time point. If only a sub5et oflesion measurements are made at an a5sessment. usu.aHy the case is also cousidered NE at that time point. unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned time point response. TI1is would be most likelyto happen in the case of PD. For example, if a subject had a baseline sum of 50 IIIIII with 3 measured lesions and at F/U only 2 lesions ·were assessed , but those gave a s1m1 of 80 nuu, the subject will have achieved PD status, regardless of the conllibution of the missing lesion.

17.3.2.4.3. Best Ove1·a ll Response: All Time Points

Toe best overall response is detennined once al1 the data for tbe subject is known.

Best response dete1mination in this study requires confmnatiou of CR or PR: Best respouse is defmed a5 the lesser of the two best responses across 2 consecutive scans (eg, a snbje ct who has PR at first assessment, SD at second assessment, and PD on last assessment; thjs would repott as a best overall 1-e.sponse of SD). \Vben SD is believed to be best response, it must also meet the protocol specified minimum time from baseline, 6 weeks(± 7 days). If the minimum time is not met when SD is otl1erwise the best time point response. rhe subject' s best response depends on the subsequent assessments. For example, a subject who has SD at first assessment, PD at second andl does not meet mini m um duration for SD, will have a best response of PD. The same subject lost to F/U after tlte first SD assessment would be considered ineva Jua ble.

17.3.2.4.4. Special Notes on Response Assessment

\Vllen nodal disease is included in the sum of target lesions a11d the nodes decrease to " normal" size (<10 mm), they may still have a measurement reported on scans. This measurement should be recorded even tlrnugb tl1e nodes are nonual in order not to overstate progression should it be based on increase i11 size of the nodes. As noted earlier, th.is means that subjects with CR may not have a total sum of "zero" on the eCRF.

Subjects with a global deterioration of heaJtl1 st a tus re qufr iug discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic dete1ioration." Every effo1t should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response: it is a reason for stopping study therapy. l11e objective response status of such subjects is to be derennined by evaluation of target and non-target disease.

For equivo cal findings of progression (eg, very small and uncert ain new lesions; cystic changes or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If at the next schedu]ed assessment, progression is contin ned, tbe date of progression should be the earli er date when progression was suspected.

17.3.2.5. Frequency of Tumor Re-evaluation

In this study, tumor measurement will be conducted every 6 weeks (± 7 days) while the subject remains on study until progression of disease, withdrawal of consent, death, or loss to F/U. Scan dates sbou]d not be adjusted or reschedu1ed due to dose inten-uption of any type.

Baseline tumor asse;5sme 11ts must be pe1formed ,vithin 28 days of em:oll.n1ent (s tudy treatment).

All efforts should be made to ensure consistency bem'een the baseline measurements and all subsequent measurementsin reference to utilization ofscanning method, equipment. techni que (includ ing slice thickness and field of view), and radiographic interpreter.

The radiographic evalu ation must iu.dude CT or MRI scanning of chest, abdomen, and pelvis at screening period. A CT or **ti.•1RI** of the brain is mandatory for aJI su'l .iects included with baseline stable brain metastases. Any additiouaJ suspected sites of disease should also be imaged. Every effort should be made to use the same assessment modality for all assessments for each subject. F/U evaluations should include aJl sites of disease identified at screening and any other locations if progressive disease is suspected (eg, CT or **lvfRI** of the brain if brain metastases are suspected} should also be imaged. A11 e valu a tion s should meet the s tandard of care for imaging of lesions in the respective orga11(s) and should confom1 to the image acquisition guidelinesaccording to institutional standards.

All targ et and non-target sites are evaluated at each time point of tumor assessment.

17.4. New York Heart Association Functional Classification

Table 17.3: New York Heal't Association Functional Classmcation

FunrtlonaJ C apacity	**Objtt tlvt Asse-s sment**
Class I. Patieuts with cardiac dis·ease but withoutresulting limitation ofphysical act ivity. Ordinary physical activity does not cause undue fatigue palpitation.dyspnea. or angina,! pain.	**A.** No objective evidence of cardiovascular disease.
Class II. Patients with card iac diseas e resulting in s1ight limit ation of physic.al activity. l11ey are comfo rt.lble at rest. Ordinary physical activity resu]ts in fati{?ue. palpita1iou. dyspnea. or augiual pain.	B. Objective evidence of minimal cardiovascular disease.
Class I II. Patients with cardiac disease resulting in marked lJm.itatiou of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue. palpita tion, dysp nea or anginal pain_	C. Objective evidence of moderately severe cardiovascular disease.
C lass IV. Patients with cardiac disease resulting iu inability to cany on any physic al activity withou t discomfort. Symptoms of herut fai lure or tl1e anginal syndrome may be present even at rest. If any pbysica J activity is undertaken. discomfo11 is increased.	**D.** Objective evidence of severe cardiovascular disease.

Source: American Hean Association. Inc. Classificationof Functional Capacity and Objective Assessment. Available from;
http:/fmy.americauheart.org/professional/StatementsGuidelines/ByPublicationDate/PreviousYean../Classificarion-of-FW1ctiona l--Capacity-and-Objective-A.ssessment _UCM_'l2381 1_All icle.jsp

17.5. Instructions Related to SARS-CoV-2

Due to the potential impact of SARS-CoV-2. ie COVID-19. on subject safety. the Sponsor reco mm end s the fo llowin g dose modification and mainage m ent plan for subjects ,vith confirmed or suspected SARS-CoV-2 while being treated with DS-8201a. Dose modifications will be based on the worst CTCAE grade. Use CTCAE version5.0 general grading crite1ia to evaluate SARS-CoV-2. All dose modificatiosn(discontinuation. interrmptiosn or reductions) must be recorded on tbe AE and dmg achui nistration eCRFs.

17.5.1. Dose- 1\1od ifkatlon C riteria for Suspected or Confirmed SARS-CoV-2

If SARS-CoV-2 infecti on is suspected, intenupt DS-820la and m]e out SARS-CoV-2 per local guidance.

If SARS-CoV-2 is mled out, follow sn1dy protocol

If SARS-CoV-2 is confinne-d or is still suspecte-0 after evaluation follow dose modification as outlined. in Table l 7.£1 below and manage SARS-Co\l-2 per **local** guidance until recovery of SARS-CoV-2.SARS-CoV-2 recovery is defined as no sig11s/sympto111s of SARS-CoV-2, at least 1 negative real-time reverse transcription polymerase chain reaction (RT-PCR) test result, aud nearly or completely resolved chest CT findings_

Table 17.4: SARS-CoV-2 Dose l\fodlfk atlon Cr lteria

SARS-CoV-2 Worst T oxi(ity **NCI-CTC.AE Version 5..0 Grade**	Sc:be d ule Modification for DS-820Ia
Grade 1	Resume srudy drug at tbe same dose[1]
Grade 2	Resume sn1dy dmg at the same dose if chest CT findin are completely resolved[1] Reduce by 1 dose level if chest CT findings are nearly resolve.cl
Grade 3	Reduce by 1 dose level if checst CT findings are completely resolved Disco ntinue shtdy dmg if chest CT findings are!!filcompletely resolved
Grade 4	Discont inue smdy dmg

SARS-CoV-2 = severe acuteres-piramry syndromecoronavim 2 (SARS-CoV-2): CT= computed tomography

• Closely monitor i;igns/symptomsafter resuming DS-8201a, initially with a phone call every 3 days for the first week. and chell \ri1ba weekJy phone call thereafter for a0 1aJ of 6 weeks.

In addition to the recommendations outlined in Table 17.4 , inv -tigators may consider dose modifications of the study dmg according to the subject's condition and after discussion with t1 1e s nid y Medica] .Monitor or desiignee.

If au event is suspectedto be dmg-related ILD/pneumouitsi, manage per protocol ILD/pneumonitismanagement guideline.

17.5.2. Prior and Concomitant Medications- Prohibited Therapies/Products

- Chloroquine or hydroxychloroquine;
  - Concomitant treatment is not allowed during the study treatment (Section 5.6).
  - If treatment is absolutely required for SARS-CoV-2, DS-8201a must be interrupted.
  - If administered, then a washout period of no less than 14 days is required before resumption of DS-8201a.

17.5.3. PK Assessment(s) if Chloroquine or Hydroxychloroquine is Administered

Additional PK sennn samples should be collected, if chloroquine orhydroxycbloroquine is administered for SARS-C'oV-2 infection , at the -time points specifie-0 in the Schedule of Events (Table 8.3).

The chloroquine or hydroxychloroquine administration time and the exact time of blood sample collection for PK analysis must be recorded on the eCRF..

17.5.4. SARS-CoV-2 Assessment(s)

.>\II confllllled or suspected SARS-CoV-2 infection events must be recorded in the eCRF. If a subject preseuts to the clinic with symptoms suggestive of SARS-CoV-2, but the RT-PCR test is not available at the site, a sample kit will be provided for sample collection to be tested at a central laborator y. Toe results will be provided to the site from the central laboratory.

Semm samples wiH be used for SARS-CoV-2 testing from each subject who provides consent. Samples wiU be collected prior to the srudy dmg infusion, shipped to a central laboratory, and stored there until the tests become available.

If subjects consen.t the remaining sem m sampk5 will also be stored for futtue analysis.

17.5.S. Statistical Analysts - Assessment of the Jmpact of SARS-CoV-2

If deemed appropriate, analyses will be performed to explore the impact of S.lul S-CoV-2 on the safety, efficacy. and any other endpoints, as al)propriate, rep011ed for the study.

As a result of the impact ofSARS-CoV-2 on studyconduct adjustments to the statistical analysis and interpretation will be made. ifrequired. These will be described in the statistical analysis plan.

18. SCHEDULE OF EVENTS

Table 18.1: Schedule of E\'ent.s

	Tissue Su1:tn	S C R	Cycle J					Cyd e l		Cyd e J		Cyd e -l a.nd s11bsN1uent cyd es Day I		EOT "	F il. "h	q3mo F /U (± 14 day)
			Day 1		Day s	Dayl5	Tut· 22	**Day 1**		Day 1						
			Bl	EOI	(± 1 da y)	(:!: I. day)	(:!: 2 dp)	Bl	1:01	Bl	EOI	Bl	EOI			
Informed Consoli	■	●														
Tumor le for IJSSUC' s"meo in.8	•															
'lew mclusionlexcll1Stm cri teria, and Resrisln tioo lo	•															
HIV annoody T (as **requiied** by local reeul) Hepalltis B e Anti nl'Jlepahbs C Amibod:}·		·q														
Arlminisler DS--810. 1a			•					•		•		•				
Medical histozy/Da:nograpbic		• d'														
Vi la1 Sign		•d	■	•	•	•		•	'	' •	•	·●·		•	•	
Pb }'\i 1< alE.'laiIJ1UI LIOU		ed	• •					• •				●●		●	●	
Sp():		•	• •							●●		●•		•	•	
Height		•														
WeiB,ht ECOG PS		,_d	••							●●		• •		•	•	

Table18.1: Scheclule of Events (Contlnued)

	n s ut Scr tt n	S C R	C 'd C' l					Cyclt 2		ck 3		C)C'IC·4 and subsequt nt crd ts Da y l		for•	F fl" b	q3 mo Fil: (.± H d1ys)
			Da y l		Day 8	D.1)· l:'I	Day 22	Day I		Dll)" I						
			Rl	F ,OJ	(± 1 d ay)	(± 1 d ay)	(± 2d lly>)	Kl	EDI	HJ	EOI	BI	£01			
Cliruc.11 La.bor itory Tests		d	••		•	•		•'		••		• •		•	•	
Tmponiil		• .i		▪ '					▪ '		. r		. r	. r	•'	
Blood Samples ford DNA												•'.t		•		
Pbe:nnaro Bbo Samp!C'			••													
PK Blood :Sa le•			•'	. V	•	•	C•ll	. ;	.i	.j	. Lk	•'	.•i			
ADA Blood Sample												•'"			•	. D
Blood Sample fur HER2ECD (y)		▪ '''										. -0		•		
Unnalysls		J														
ECHO or MUOA (LVEF)		. "l										•'		•		
12-1-1 ECO ID tnpllcate-[1]								♦ '4'		••·P		· ,,p		•		
Ophiba.Imologtc Asses.		◆'1						●				•'		•		
.Pregi:wlcy Test		•"								•"		• •		•	•	
TuulOr.Asses:smeDl		•q·v	•V faery 611„ce.ks (7 days) will PDor stltlllll8 tlewa:ulie lllCcr trcallle1ltreganlless of Post Trestwenl Follow-up period											•		
FTesh tumorsm.,le									• Atday 43 (-:t: 7 da)".'i)							
Cmreomitenl Medication'i/ Afa			•													
sllP;, ,al Ftu																•

ADA= anti-drug antioody. AE = adverse event. BI= fore infusion.cfDNA = cell free deoxyiibonucJeic acid.COVID 19 = coronavims djsease2019. CT= computed 10mogn1pby. ECG= electrocardiograni ECOG PS= Ea.stem Coope ralive Oncology Group perfomiance status. ECHO= echocardiogram , E Ol = end of infosion. EOT = end of treatment. F/U: follow-up. HE R2ECD = extracellular <lomain of HE R2. ICF = informed consent form. IXRS = interactive web/voice response system. MUGA = mulligated acquisition. MRJ = magnetic r e,;onance imaging. L\i"EF = left ventriculai·ejection fracti011- PD= progressive dis.ease. PK= phen nacokiuetic. SpO =peripheral oxygen saruratiou. q3 mo = ooce ewty *3 m*md, s. SCR =scre en in g

a. The date wheu the investigator decides lo discontinue study treatment (+7 days)
b.40 days (+ 7 days) after the last study dmg administration or before starting new anticancer tre.atme:n t, wbichevei- comes first
c. Three l)pes of infonned consent are pllepared by tbe spo nsor. If tbe si te use the ICF for "tissu e sc reening," it should be obtained befOl'e ohtaiuiug tumor or submittingnunor to the ceutraJ laboratory.
d. Within 14 days'before Day I on Cycle I
e. Within 3 days before adm.inistration
f. Troponiu (preferably higl1-sensitivitytroponin-T) shoul d be co lle-cted at screening and Day I of eveil'y Cycles, EOT and F/U at 2 to J hours after end of infusion as per the table above. [f elevated, or detected., refer to Section 6.4. l. n 1e test used to test t:roponin s bould remain the i;ame throughout tbe course of **a** subject's time on study. An additional sample should be submitted for central lab troponin-T testing
g.Samples wiU be colle et ed at BI on Day I of Cycle I. Cycle4 and EDTfor cfiJNA.
h.Participation in this paI1of thestudy is optional for all subjects.
i. - 8 to 0 hours BI 011Day I of each cycle until Cyde 4 and in Cyde 6.
j. Within 15 minutseofEOI onDay I of each cycle until Cycle 4 and in CycJe 6.
k.4 **b** (± 15 minu tes) and 7 h (± 2 hours) after the sta11 ofa d m.inis t:ntt io n
I. If treatment of the next cycle is delayed for 3 days or longer. or the subject is discontinued. collect PK blood on this day(± 2 days)
m. - 8 toO hoursBI on Day 1 of CycJes 1, 2 and 4, and then every 4 cycles
n.For subjC\:ts v.itb positive ADA at the F/U "is.it. a dditi onal se rum ADA S,!!IDples may be co llected eveJy 3 tuo11ths (± 14 da ys) up to I year afh:r the las t dose of the studydrug., or until tihe ADA becomes negative. or lUJtil tl1e ADA titer becomes less than t]1e baseline{applicable wheu pre--e.--.istiJ1g ADA i;vas o bsef\' e d), or until the su bjec t starts another tbc rapy for cancer or wi.thdra 'Ars consen t from the study, ,,,hic hcvcr ocnlf'S first.
a. Every 2 cycleS from Cycle 3 (eg, Day 1 of Cycles 3, *5*,,7 **9...).**
p.Before administration at every cycles
q. Within 28 days befol'e Day! on cycleI _
r. ECHO or MUGAscan ru.sessmen ts will bepe1fonned al Sc1·eening and BI on Day I of Cycle *5* and I hen ev<:ry 4 cycles(:1:. 7 days) (eg. Cycles *5*,9, 13...)
s. ECGs will be taken in dose succes.sion while in a supine.Jsemi- rec um bem positiou
t. OphthalmoJogic as.ses.!·>meots including visual acuity tes tin g. slit lamp examination and fundoscopy will be perfonned on Day I of Cycle *1* (•w-ithin 3 days before administration) and evety 4 cycles *(:1:.1* da ys) there after (eg, Day I of cycle!> 2. 6. 1,0 14...).
11.Within 72 hours prior to enrolJment (snidy treatment)
v. A CT or MRI of the brain is to be included for all subjec1s at SCR. Subjects will1out brain metastases do not need additionaJbrain scans for tumor assessment LU1!ess clinically indicated. Sc.ans of the chest abdomen pel vis and any other siles of disease are n q uested.
w. Obtain fresh tumor biopsy specimen:fi:om a subject. Fl'esh biopsy is not needed if a sample that was obtained after the most recent anti allcer therapy is already available.
x. In.case of admini tratiollof chioroquin.e.ihydroxycWoroquine. perfonu PK sampling according to the foUowing ch.edule : pre-dose on Day 1 of chloroquinehydroxychloroquineadminisrration, pre-dose Oil Day 3 or Day -t (±4 hours). end of chloroquinehyd!roJ-ychloroquinetreatment (±4 hours}. and after washout period (14 days) pre-dose Oil the day of restartingsmdy treatmem (±& homs) (Table 8.3).
y. A pot1ion of HER2ECD blood sample fromeach subject who provides consent will be used for fnrure central lab analysis for SARS..CoV-2 testing. SARS-CoV-2 tse ting will be conducted every 4 qdes from Cycle 5 (cy cles 5, 9, 13. de) and EOT.

For suspected ILD/pneumonitis. treatment with study chu g sho uld be in tem rpted pending evalua tion.
Evaluations shouldinclude:

- high resolution CT
- pulmooologist consultation (Infec tious Di sease consultation as clinically indicated)
- Blood culture and CBC. Other blood tests could beconsidered as needed
- Consider broncboscopy and bronchoalveolar lavage if clinically indicated and feasible
- pulmonary function tests and pulseoximetry (SpO,)
- arterial blood gas es if cliuic.ally indic.ated
- one blood sample collection for PK analysis as soon as ILD/pneuw.onitis is suspected, i.f feasible.

Other tests could beconsideJed. as needed.